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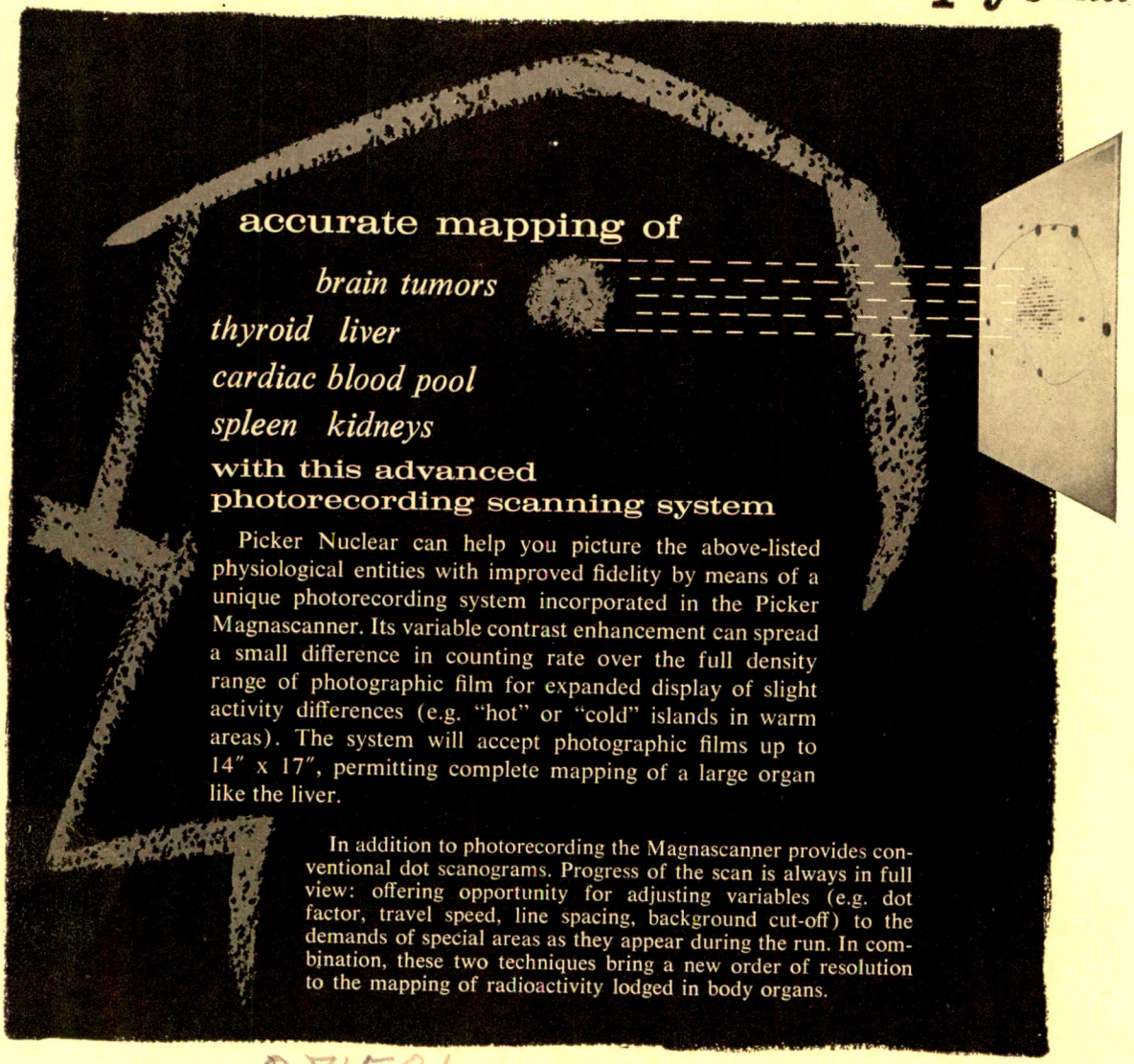
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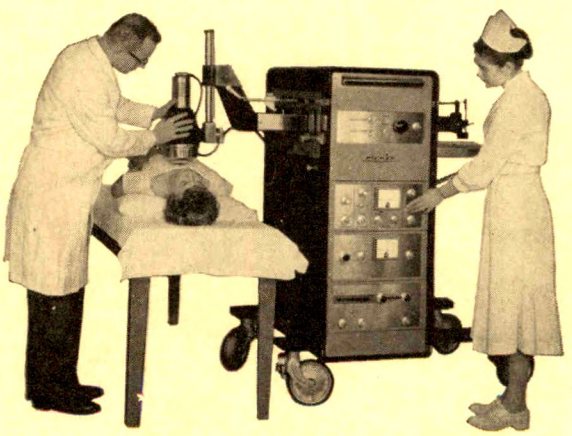
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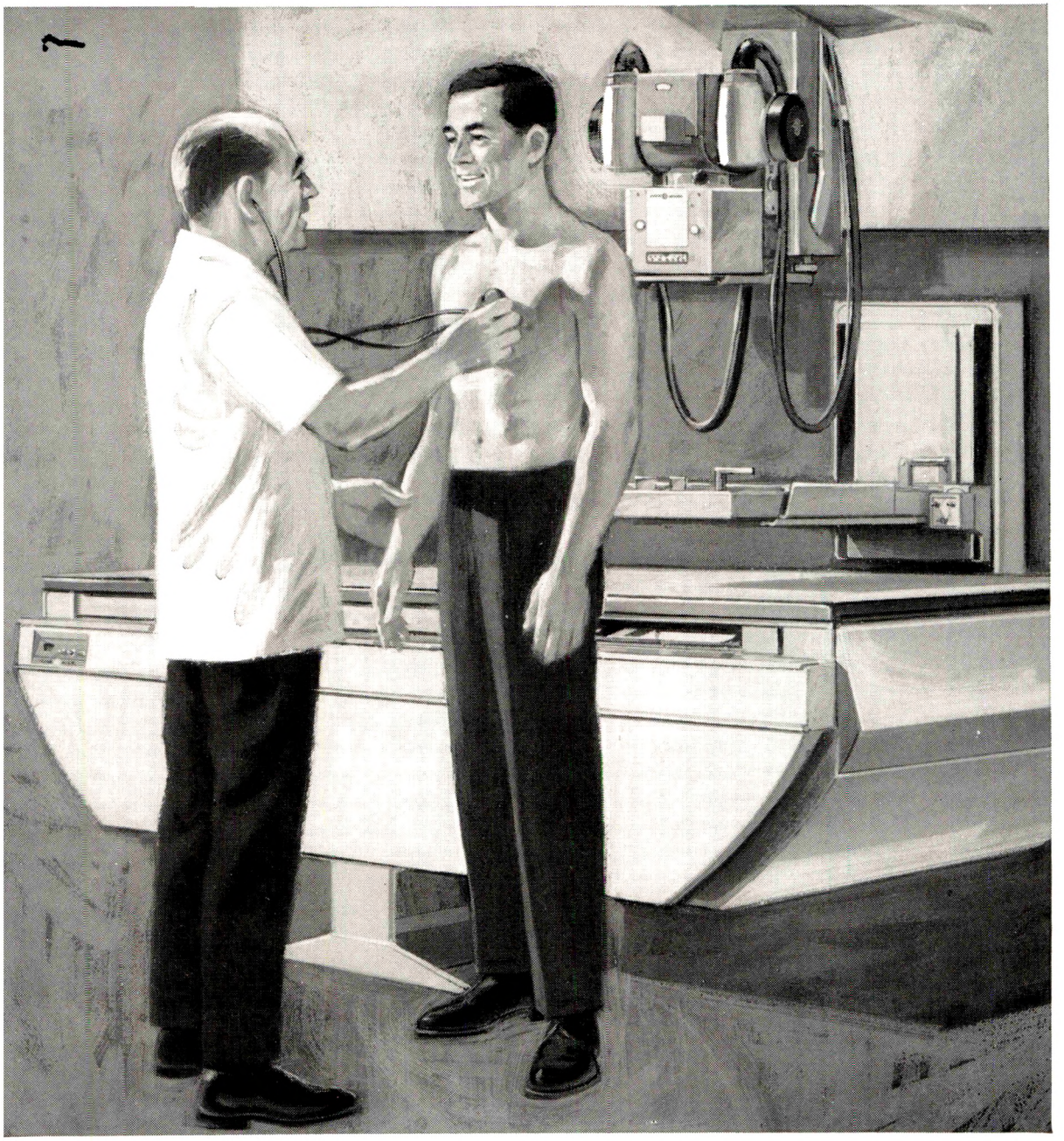
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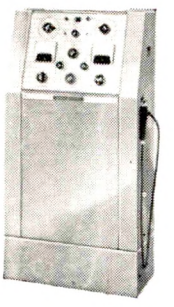
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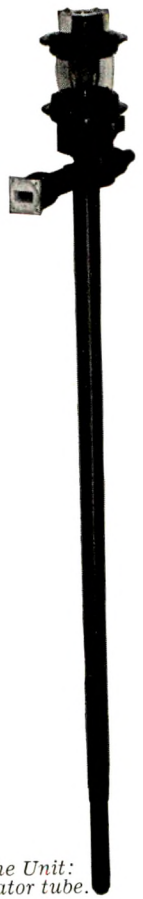
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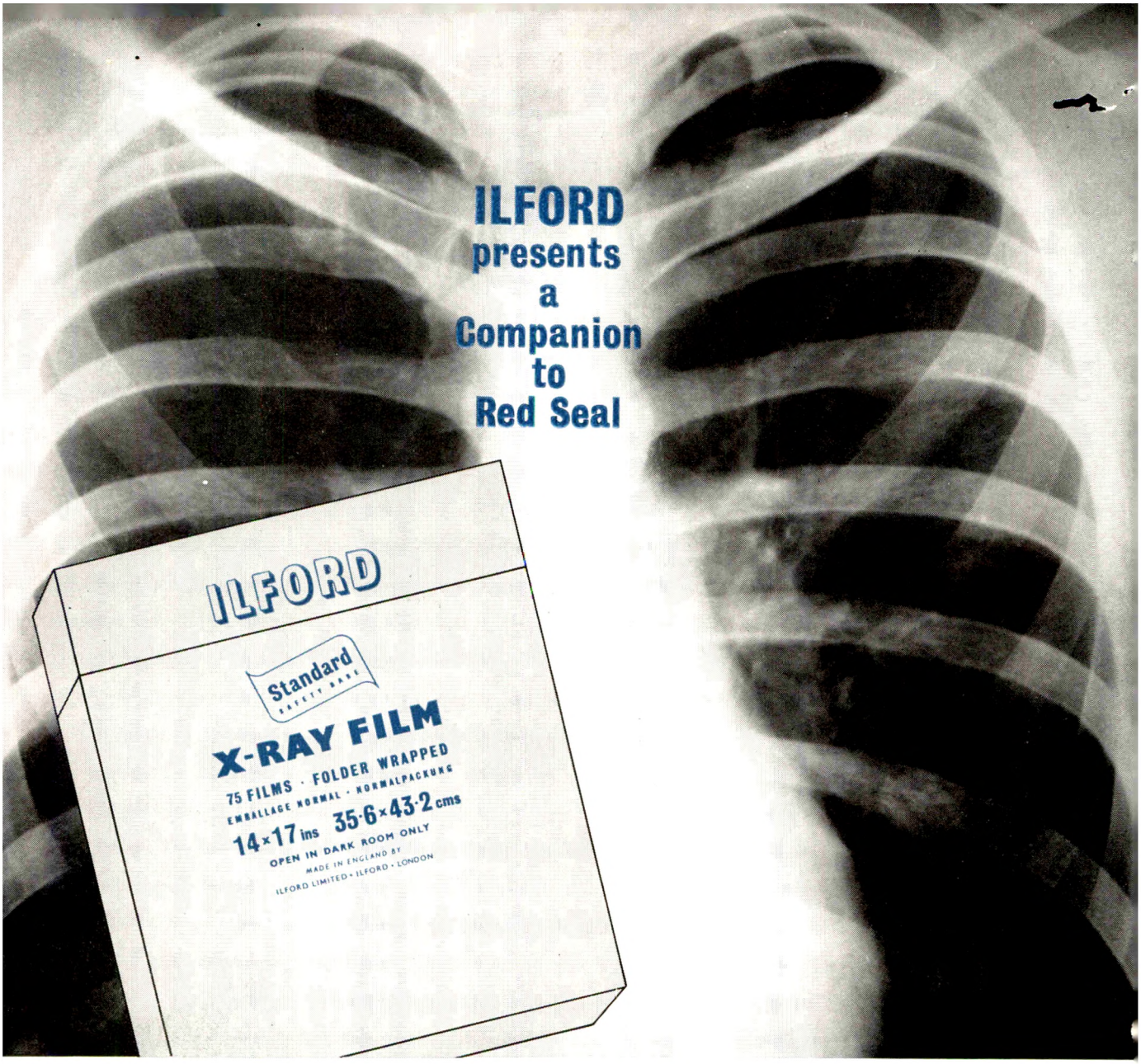
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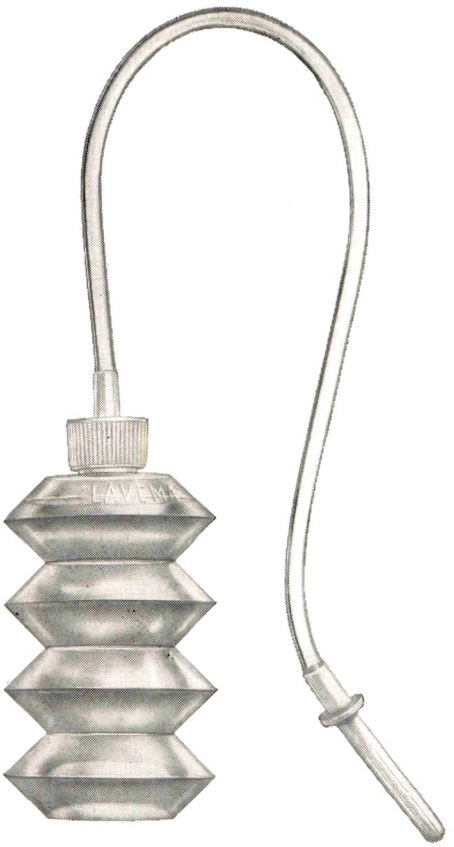
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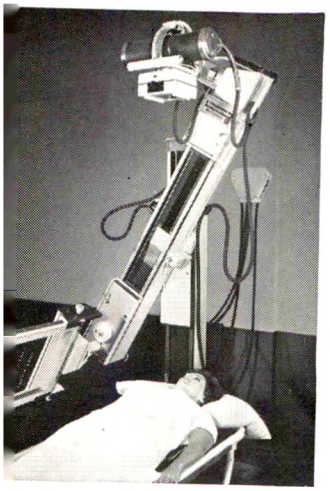
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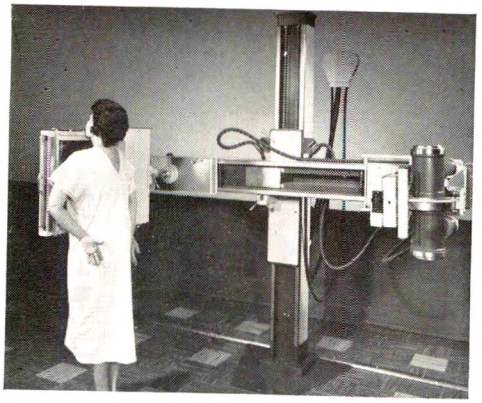
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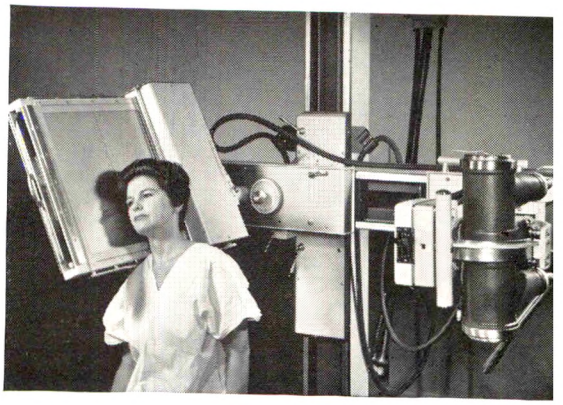
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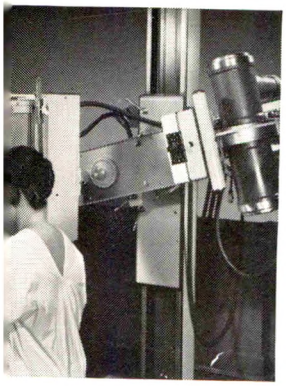
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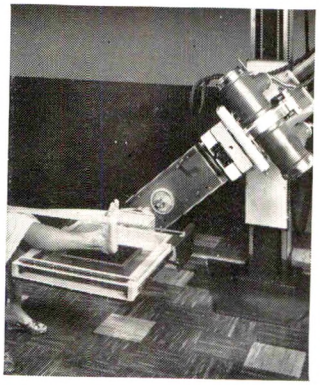
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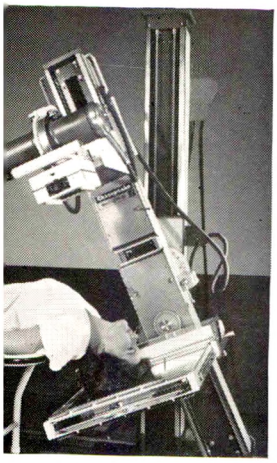


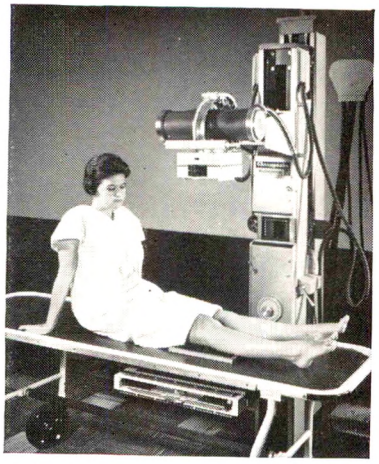


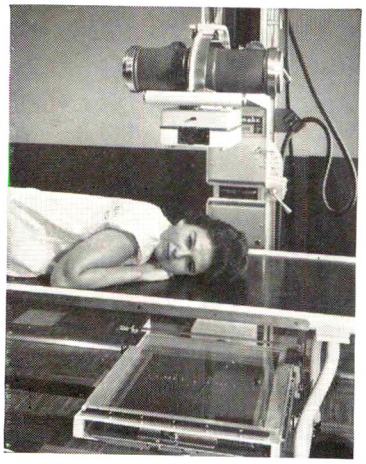


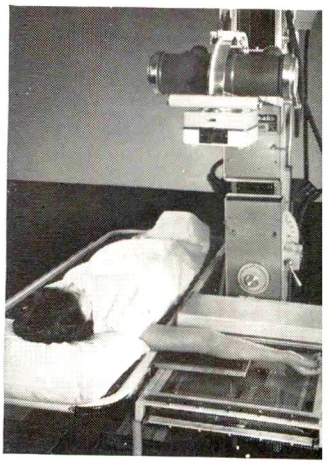


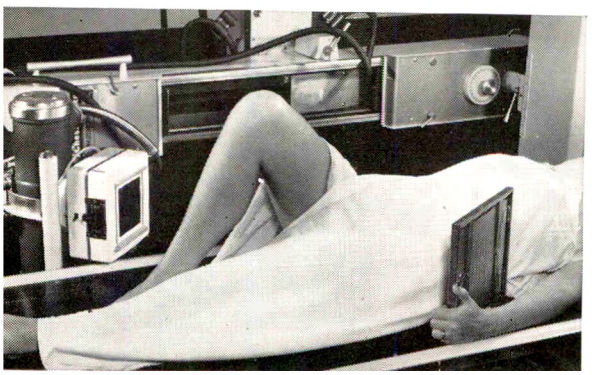












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GIANT HYPERTROPHY OF THE GASTRIC MUCOSA (MENETRIER'S DISEASE): A CORRELATION OF THE ROENTGENOGRAPHIC, PATHOLOGIC, AND CLINICAL FINDINGS*

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ROCHESTER, MINNESOTA

GIANT hypertrophy of the gastric rugae, originally described by Menetrier[5] in 1888 is a fairly specific pathologic entity with characteristic gross and microscopic findings confined to the gastric mucosa. Its cardinal feature is a remarkable enlargement of the gastric rugae, which become contorted and folded on one another in a convolutional pattern reminiscent of the gyri and sulci of the brain (Fig. 1*a*). The hypertrophy may involve the mucosa of the entire stomach, except for a narrow zone along the lesser curvature, or it may be confined to a small region sharply demarcated from adjacent normal gastric mucosa (Fig. 1*b*).

Microscopically, the gastric glands in the involved area are increased in length and number but they contain normal proportions of specialized cells. They may, at times, exhibit tortuosity and dilatation, minor degrees of cyst formation, edema, and inflammation. With rare exceptions, the glands do not invade the muscularis mucosae.

Because of its rarity and its ability to simulate other more serious afflictions of the stomach, the condition has almost invariably escaped preoperative recognition.

Gastric biopsy has sometimes given positive results, but just as often biopsy has been misleading because the specimen was inadequate or an uninvolved area was excised. In the past, the diagnosis of Menetrier's disease has been almost always made in the laboratory of the surgical pathologist.

The etiology is obscure. No constant relationship exists between the disorder and any of the etiologic factors mentioned in the literature, such as alcohol, nicotine, sepsis, deficient diet, heredity, or viruses.

* Abridgment of thesis submitted by Dr. Reese to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Radiology.

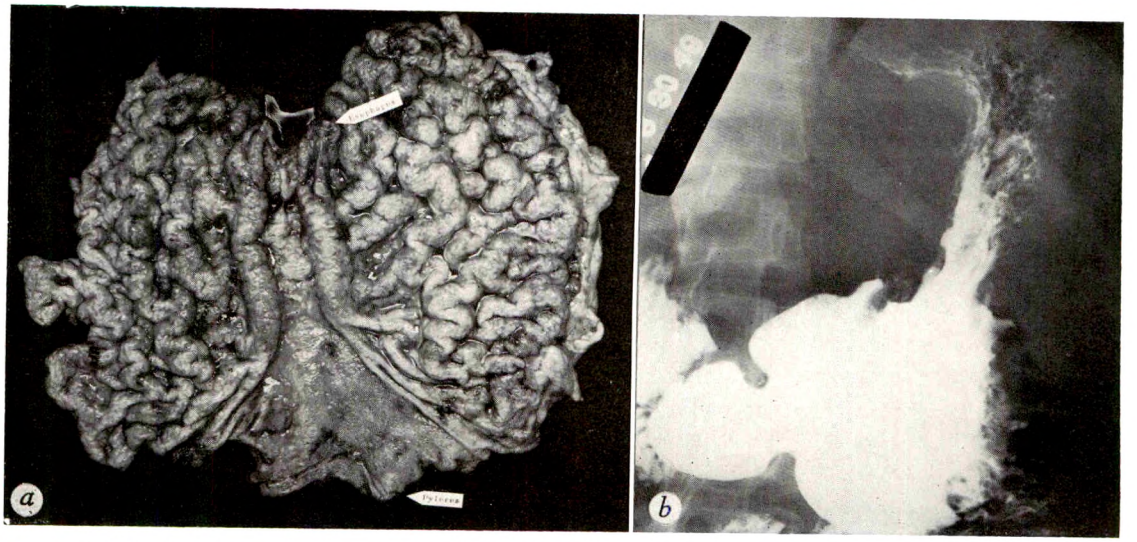


FIG. 1. (*a*) Fixed specimen. The massively enlarged folds give the mucosa of the stomach a resemblance to the brain. Notice the sharp demarcation between the uninvolved antrum and the remainder of the stomach. (*b*) Roentgenographic appearance of stomach shown in Figure 1*a*. There is a filling defect along the entire greater curvature. Notice that the antrum appears quite normal. Wall thickness as measured on this film was 25 mm.

In recent years the association of multiple endocrine adenomata has been mentioned.[6,7] Two of Underdal *et al.*'s 8 patients with multiple endocrine tumors had giant hypertrophy of the gastric mucosa.[7] Schlaeger *et al.*[6] considered the association of the two conditions not unusual. Also, Menetrier's disease is often associated with hypoproteinemia, sometimes profound enough to cause peripheral edema. Citrin *et al.*,[1] in 1957, reported that 16 of 23 patients, on whom protein determinations were made, had hypoproteinemia; all had normal albumin-globulin ratios. Using radioiodinated serum albumin, Citrin *et al.* found a small albumin pool with a rapid turnover. Loss of albumin into gastric juice or mucus and subsequent digestion were more rapid than albumin synthesis.

Giant hypertrophy of the gastric rugae is rare. Only 80 cases, verified pathologically, were reported by 1960. It is probably more common than this figure would indicate, however, because many patients with enlarged rugae, as seen roentgenographically, are not operated on. The fact that some 30 cases have been described during the past 10 years suggests an increasing awareness of the condition.

Patients range in age from 20 to 70, and most are in the fourth and fifth decades. Men are more often afflicted than women; the ratio varies from 2:1 to 3:1 in most series.

The clinical picture is not specific. In Fieber's substantial review of the literature,[2] pain was a cardinal symptom in 74 per cent of cases, loss of weight in 60 per cent, vomiting in 42 per cent, and hemorrhage in 20 per cent. In the 20 cases analyzed by Kenney *et al.*[3] 11 had ulcerlike symptoms, seven had loss of weight, and two were asymptomatic.

MATERIALS AND METHODS

In order to collect this series of cases of Menetrier's disease, Mayo Clinic records of patients seen from 1949 to 1960, bearing the diagnosis of acute, chronic or hypertrophic gastritis, Menetrier's disease, or enlarged gastric rugae were reviewed. Only those cases seen from 1949 to 1960 were included because roentgenograms made before 1949 were unavailable. Of 158 case records thus obtained, adequate gross, microscopic, and roentgenographic mate-

rial was available for only 18 patients, who met all the criteria for the diagnosis of Menetrier's disease. These 18 patients had had total or subtotal gastrectomies; formalin-preserved specimens were available for study in each instance.

Five cases in the present series were previously reported by Kenney *et al.*[3]

FINDINGS IN THIS STUDY

Gross Pathologic Features. The giant rugae involved the greater curvature of the stomach in each of the gross specimens; in no instance did they involve the antrum or the lesser curvature. There was always an abrupt demarcation between normal and abnormal folds. The proximal half or two thirds of the stomach was more or less diffusely involved in 15 cases. An isolated area of the mucosa of the greater curvature was involved in 3 cases.

Gastric ulcers, less than 1 cm. in diameter, were found in 13 specimens. In one instance a carcinoma was found in an ulcer of the antrum which looked benign. This ulcer was 3 cm. from the area of giant folds in the proximal portion of the stomach. The association of the two lesions was probably coincidental.

In one instance, a Grade 1 islet cell adenocarcinoma of the pancreas was associated with Menetrier's disease.

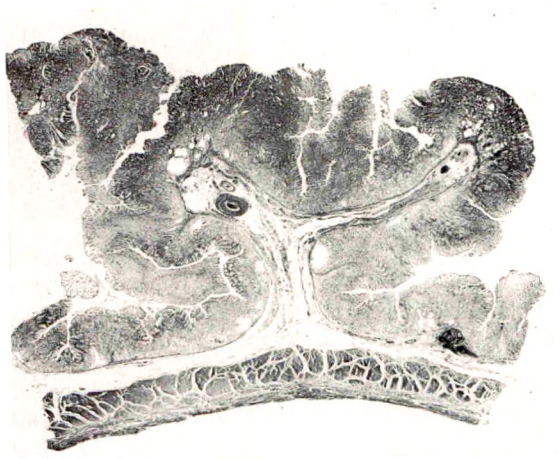


Fig. 2. Under low power the abnormally thick mucous membrane is readily appreciated. Seen here is one large branching fold (hematoxylin and eosin; ×5½).

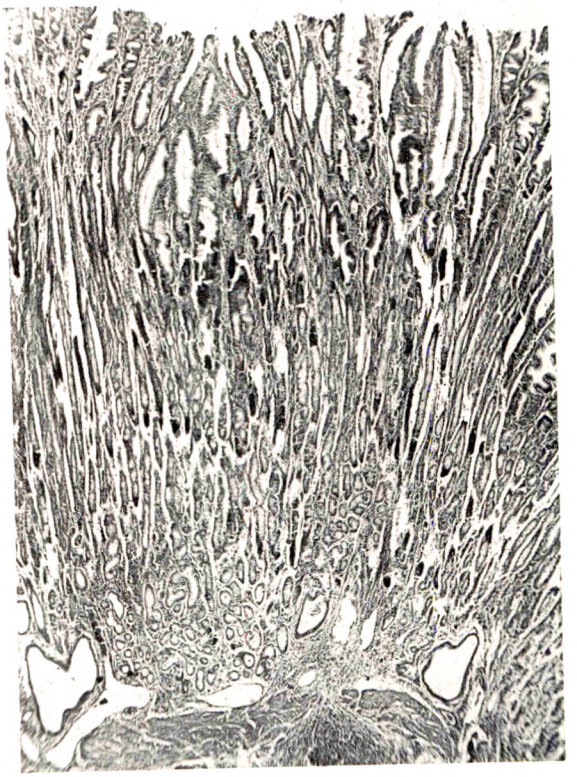


Fig. 3. (Same case as Figure 1.) Under higher power the abnormally elongated glands can be seen. The coiling at the base of the glands and the cyst formation are noteworthy. The glands are otherwise normal except for some mucus plugs in the gastric pits. Notice that the glands do not involve the muscularis mucosae (hematoxylin and eosin; ×23).

Microscopic Features. The abnormally thick mucous membrane, easily seen with the naked eye, measured up to 5 mm. in thickness, whereas normal mucous membrane measures 0.3 to 1.5 mm. The furrowing and heaping up of the mucous membrane above the normal muscularis propria furnished a large increase in the mucosal lining of the stomach (Fig. 2).

Under objectives of higher power, the gastric glands were seen to be increased in number and in length (Fig. 3). The glands usually contained a normal proportion of parietal, zymogenic, and mucous cells, although in a few instances there was an increase in the relative number of parietal cells. Frequent excessive coiling of the

glands and occasional cyst formation were seen at the bases of the glands. In no instance did the glands penetrate the muscularis mucosae.

Clinical and Laboratory Features. At operation the ages of these patients, all men, ranged from 24 to 61 years. The average age was 46 years.

Epigastric pain or distress of fairly long duration, with or without nausea and vomiting, was the most typical presenting complaint; 14 patients (78 per cent) complained of it. Nausea and vomiting were mentioned in 9 (50 per cent) of the case histories, and frank hematemesis in 2 (11 per cent). Only 5 patients (28 per cent) had histories of gastrointestinal disturbances lasting less than 1 year. In the remainder the symptoms had been present for 2 to 30 years. Eight patients (44 per cent) had lost 10 pounds or more.

Except for occasional epigastric tenderness and an instance of peripheral edema associated with severe hypoproteinemia, physical examination was unremarkable.

Hemoglobin measured less than 13 gm. per 100 ml. in only three instances. Gastric acid determinations, performed on 14 patients, only once revealed histamine-fast achlorhydria. The erythrocyte sedimentation rate was normal in six instances. In no case was it strikingly high, as might be expected in gastric malignancy. Protein determinations on 11 patients disclosed abnormally low values in 8 patients. In one instance there was a reverse of the albumin-globulin ratio.

RETROSPECTIVE STUDY OF THE ROENTGENOGRAMS

The roentgenograms in these 18 cases were examined and compared in the hope that some group of abnormalities could be found which would improve the rather poor diagnostic accuracy mentioned earlier. A group of four such abnormalities was found. Although no single sign was pathognomonic for this disease, various combinations of the four strongly suggested the correct diagnosis. The four abnormalities concern the following: (1) size of gastric folds, (2) configuration of the greater curvature, (3) thickness of the stomach wall along the greater curvature, and (4) pattern produced by mucus-barium mixture.

Size of Folds. Enlargement of gastric rugae is the *sine qua non* for the diagnosis of Menetrier's disease. Typically, these folds are thick, tortuous, and angular with no uniformity of pattern or of direction. As usually seen after the ingestion of barium, they have a peculiar mottled appearance roentgenographically (Fig. 4*a*). Sometimes they are seen when air is the contrast medium. In five instances in our series enlarged folds in the cardia were seen directly by air-contrast. The rugae in this region are normally very irregular and convoluted, but they are not massive and thick.

On review of the roentgenograms made after the ingestion of barium in our 18 cases, enlarged folds were clearly seen in only eight instances and in only two did they strikingly reflect the gross appearance of the surgical specimen (Fig. 4*b*). Fluoroscopy, accompanied by palpation and compression of the stomach, demonstrated enlarged folds best.

At least three factors contributed to the poor demonstration of the rugae in the roentgenograms. First, the roentgenograms were usually made after 8 oz. of barium had been ingested, too much barium to afford a good mucosal relief pattern. Second, the abnormally thick layer of mucus effectively filled the narrow crypts or furrows between the enlarged folds, thus preventing the barium from entering these spaces. Third, the enlargement of the folds sometimes placed them in such tight apposition with one another that only those portions which were directed toward the gastric lumen were visible.

Fluoroscopically, these problems disappear because smaller amounts of barium are used, barium flows into the sulci between the folds as mucus is dislodged during palpation, and folds in tight apposition can be separated by manipulation. It should

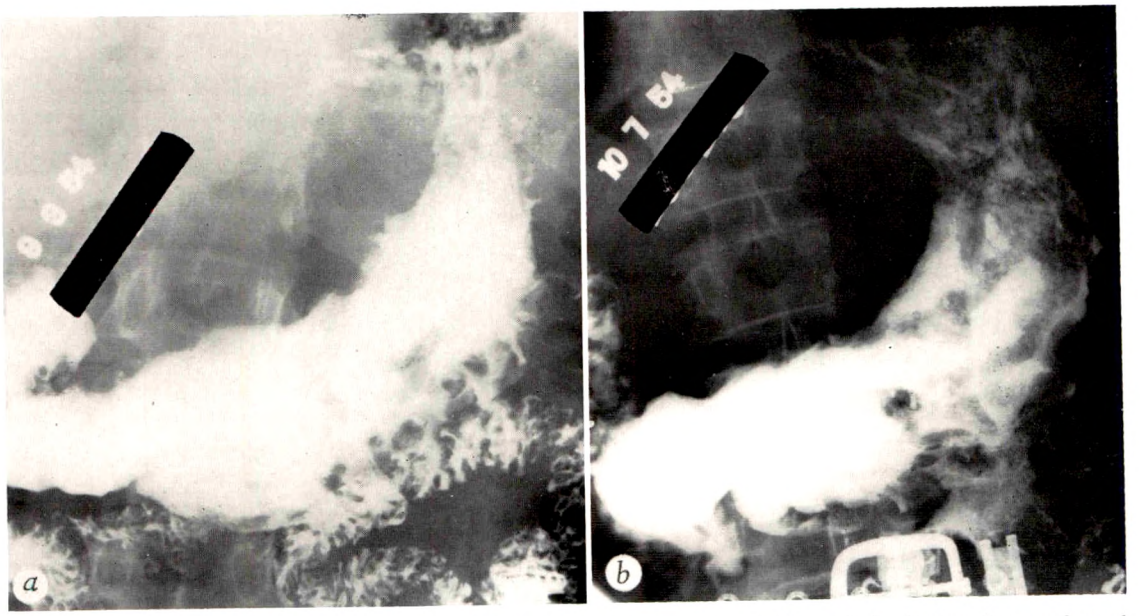


Fig. 4. Appearance in two cases after ingestion of barium. (*a*) Dimly seen through the barium is an enlarged fold running in an abnormal direction perpendicular to the long axis of the stomach and extending to the lesser curvature. The greater curvature seems to be involved in a polypoid tumefactive process. The antrum is characteristically spared. (*b*) Enlarged folds when seen give a spectacular appearance. A mottled mucus-mixing pattern is seen on the enlarged folds and in the upper portion of the stomach. The process does not extend beyond the incisura angularis. This patient had undergone gastroenterostomy 3 years previously and a stomal ulcer was found at reoperation.

be possible, therefore, to demonstrate these folds fluoroscopically in almost every instance.

Configuration of the Greater Curvature. The roentgenograms gave tangible and accurate secondary evidence of the large folds in most instances. This evidence was the ragged, nodular, crinkled appearance of the greater curvature, seen exclusively above the incisura angularis. At first glance, this resembled the picture of a large polypoid carcinoma; the greatly enlarged folds, when seen on end, looked like polypoid defects along the greater curvature. Commonly seen, perpendicular lines represented spicules of barium, trapped by apposed folds. The tips of these barium lines were often blunted, clubbed, or even forked when a pocket of barium was trapped at the base

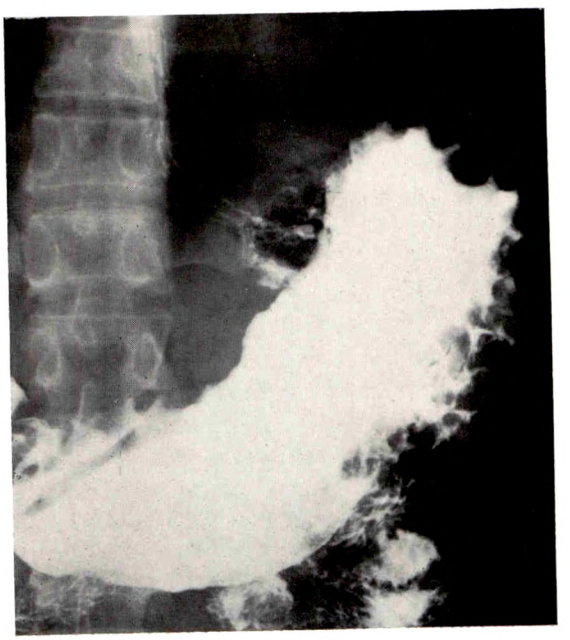


Fig. 5. Typical configuration of greater curvature. Barium has insinuated itself between the enlarged folds along the greater curvature to form rather coarse septal lines, some of which are clubbed or forked at bases of the sulci. Again, the process halts abruptly along the greater curvature as it approaches the distal end of the stomach. No abnormal folds or mucus mixing is apparent.

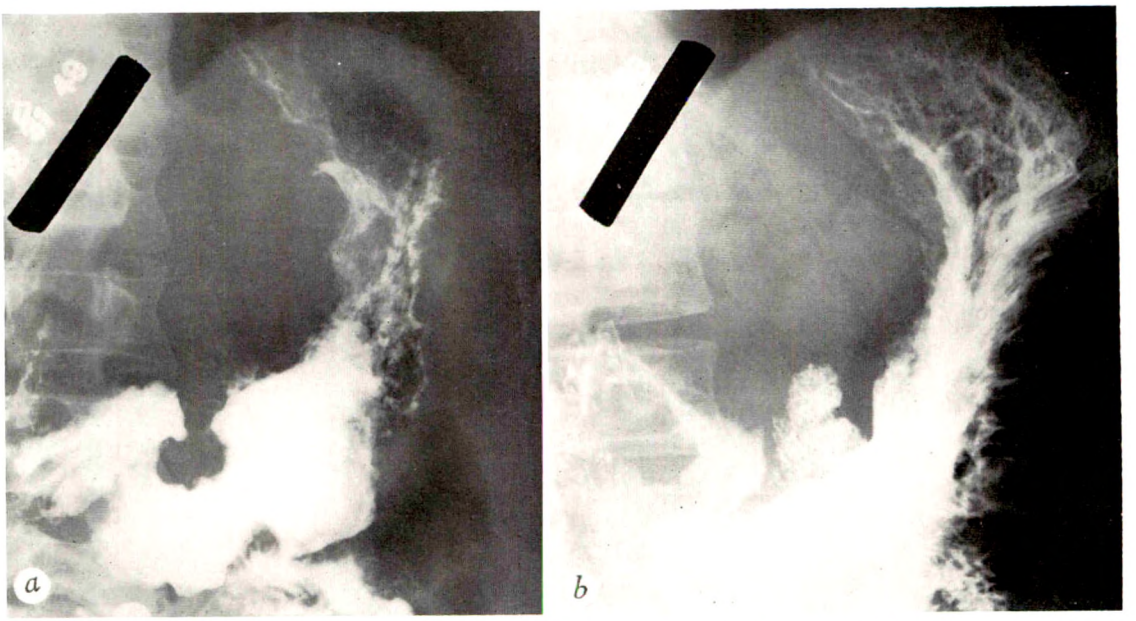


FIG. 6. Additional abnormal features in two cases. (*a*) The abnormal thickening of the gastric wall may be faintly seen along the greater curvature. Mucus mixing is prominent, but no large folds are seen. (*b*) No enlarged folds are visible. The mucus-mixing pattern is striking. It has a fine, brushed on appearance in the middle third of the stomach and a mottled and reticular appearance in the proximal third. Very fine spicules of barium are seen extending deep into the sulci of the folds along the lower portion of the greater curvature.

of one of these deep sulci (Fig. 5). Even though the giant rugae could not be seen, one could arrive at a rough estimate of their height by measuring the length of these lines.

Bearing in mind that the greater curvature is normally irregular to some extent, it was thought to have an abnormally nodular and spiculated appearance in 15 of the 18 cases (83.3 per cent). This was the most constant single roentgenographic finding in this series of patients.

Thickness of Gastric Wall. By measuring the distance between the faintly lucent serosal line of the greater curvature and the barium column within the stomach, an approximation of the thickness of the gastric wall could be obtained (Fig. 6*a*). In seven instances this measurement was greater than 10 mm. and in seven it was less than 10 mm. The serosal line was not visible in 4 cases.

Melamed *et al.*[4] presented 2 cases of infiltrating carcinoma of the stomach in which roentgenograms indicated only thickening and stiffening of the wall of the greater curvature. There was no nodularity of the greater curvature in either of these cases.

Mucus Mixing. As noted above, enlarged folds are not always seen in the roentgenogram partly because of the excess mucus in the stomach. This copious amount of mucus, however, produces its own peculiar picture which we call "mucus mixing."

In a normal stomach, a small quantity of barium will spread out over the thin layer of gastric mucus and form a smooth, homogeneous film, nicely outlining the gastric rugae. In Menetrier's disease, on the other hand, the barium mixes with an excessively thick layer of possibly abnormal mucus. The result is a striking change in the barium shadow. We observed a fine reticular pattern which, on close inspection, was often seen to be composed of an opaque shadow regularly interrupted by numerous small spaces. Sometimes the pattern resembled delicate, parallel, brush markings (Fig. 6*b*).

Also, a mottled appearance could sometimes be seen. It was somewhat similar to the mucous membrane pattern denoting a deficiency state in the small bowel, but was much finer and more uniform. This pattern may be obscured by an excess of barium. These abnormal barium patterns were observed in 14 cases. In 11 of the 14, the pattern was considered to be striking.

There was no correlation between the degree of mucus mixing and the levels of serum protein.

COMMENT

Menetrier's disease is a benign gastropathy not readily differentiated from certain other diseases by clinical or laboratory means. Its importance lies in its ability to mimic gastric neoplasm, particularly lymphoma, roentgenologically and gastroscopically. In 6 of our 18 cases the diagnosis was accurate. A tumor, carcinoma or lymphoma, was the primary diagnosis in 7 cases. In the remaining 5, gastric ulcer, antral spasm, or retained secretions were mentioned to the exclusion of Menetrier's disease.

Patients with lymphoma may present symptoms or signs of a filling defect, a gastric ulcer, an obstructing antral lesion, or a more or less diffuse infiltrating process with thickening of mucosal and submucosal structures.[8] The latter, although rare, may duplicate in almost every respect the roentgenographic picture of Menetrier's disease. If the lymphoma manifests itself as enlarged rugal folds in the *distal* half of the stomach and *along the lesser curvature* or if there is loss of pliability of the walls, then Menetrier's disease should not be considered primarily. If, however, the stomach is pliable, if the process stops at the incisura angularis and spares the lesser curve, and if the apparent nodularity can be demonstrated to represent long tortuous folds, then Menetrier's disease is probably present, especially if there is excess mucus.

Carcinoma of the stomach should seldom present much of a problem in differential diagnosis. The usual forms are either fungating, ulcerative, or deeply infiltrating. None of these enlarge the gastric rugae diffusely. The possibility of a polypoid carcinoma of the cardia cannot be excluded, when Menetrier's disease involves that area, because the cardia cannot be palpated to prove the rugal origin of the defect (Fig. 7).

Leiomyoma, leiomyosarcoma, ectopic pancreas, and prolapsing antral mucosa are associated with roentgenographic findings that are completely dissimilar to those seen in Menetrier's disease.

Acute gastritis with edema and cellular infiltration of the submucosa and lamina propria mucosae may manifest large rugae, but these should regress with appropriate treatment, while Menetrier's disease is known to have remained stable for years. Also, in acute gastritis the mucosa may be severely involved; this rarely occurs in Menetrier's disease.

Enlarged or nodular folds, roentgenographically mimicking Menetrier's disease, may occur in chronic gastritis with lymphocytic infiltration, edema, cyst formation, and fibrosis.

Wohl and Shore[9] showed that gastric

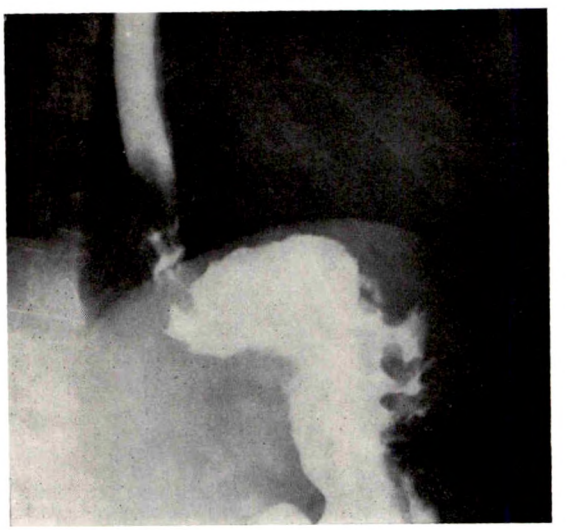


Fig. 7. Coarse polypoid or tumefactive appearance of enlarged folds high on the greater curvature. Palpation of this area at fluoroscopy would be difficult, and a true polypoid lesion in this area could not be ruled out with any certainty. No mucus mixing is seen.

varices produce a bubble-like appearance near the cardia, and they may extend along the lesser curvature, where Menetrier's disease is rarely seen. If the fundus and greater curvature are involved, the roentgenographic distinction may be difficult, but the clinical picture, the presence or absence of mucus mixing, and the presence or absence of esophageal varices should serve to distinguish one from the other.

SUMMARY AND CONCLUSION

Giant hypertrophy of the gastric rugae, Menetrier's disease, is a relatively rare disease of the gastric mucosa characterized by greatly enlarged gastric rugae, hyperplasia and hypertrophy of the gastric glands, and an excess of gastric mucus. Clinically it ordinarily manifests itself by an ulcerlike syndrome, but it may be asymptomatic.

Although the etiology is unknown, it has been associated with tumors of the ductless glands and with hypoproteinemia. Malignant disease has occasionally coexisted, but the disease is not thought to be premalignant.

Case histories, roentgenograms, and formalin-preserved specimens of the stomachs of 18 patients, all men, comprised the material for the present study. Epigastric pain and distress of fairly long duration was the most frequent complaint. Two patients experienced hematemesis, and 8 lost 10 or more pounds. Epigastric tenderness was usually noted on physical examination.

No single roentgenographic sign proved to be pathognomonic; but various combinations of the following suggest the diagnosis: enlargement of the mucosal folds, irregularity of the greater curvature, thickening of the gastric wall, and a peculiar reticular pattern produced by barium mixed with large amounts of mucus.

Giant rugae involved the greater curvature in each instance and the antrum and lesser curvature in no instance. The mucous membrane measured up to 5 mm. in thickness, and the gastric glands were increased in number and length.

Differentiating Menetrier's disease from a diffuse infiltrating lymphoma, a polypoid carcinoma of the cardia, or chronic gastritis is sometimes extremely difficult.

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Vol. 88, No. 4

GASTRITIS: A MEDICAL DILEMMA*

By LEONARD BERLIN, M.D.
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FEW diseases in medicine have as long and as controversial a history as does gastritis. Ever since Stahl first introduced this term in 1728, numerous authors have studied and argued about the matter in the literature.[11]

To review this long and interesting history is beyond the scope of the present paper. For an excellent review of the subject the reader is referred to Schindler's[35] work.

For our needs here we may start with the dawn of the contemporary era of gastritis, or more specifically with the discovery of the gastroscope. This instrument, introduced to the world by Rudolf Schindler in 1922, for the first time allowed the normal, functioning stomach to be viewed in "living color"—it permitted the pathologic variations to be photographed and preserved for all to see and to discuss. At once, considerable impetus was given to the recognition and diagnosis of various gastric diseases, especially gastritis. In 1937, Schindler[36] predicted, "the diagnosis of chronic inflammations of the stomach will probably be the most important function of gastroscopy." Events during the following years seemed to bear this out. Gastritis was being diagnosed by means of gastroscopy in patients who would never have had the disease diagnosed by any other means. Roentgenographic findings were correlated with the gastroscopic image, and as a result the criteria for the roentgen diagnosis of gastritis were formulated.

Schindler,[35] in his book on gastritis, stated, "gastroscopically, the diagnosis of chronic gastritis usually can be made without ambiguity." Vaughan *et al.*[43] in 1951 studied 41 cases of chronic enlarged and tortuous folds associated with irregular contour, abnormal peristalsis and hypersecretion. They concluded that all cases represented chronic gastritis because all had gastroscopic evidence and characteristic clinical symptoms for the condition. However, only 8 of the cases had biopsy verification. Thus, primarily because of gastroscopy and studies of this type, the classic roentgen signs of chronic gastritis were described. As Stampfli[39] in 1952 pointed out, these include thickened gastric rugae, supposedly representing swelling of the mucosa, and hypersecretion, supposedly indicating inflamed, weeping mucous membranes. Many workers[27] emphasized the importance of gastroscopy and even today several authors[3,12] refer to the substantiation of roentgenographic or clinical diagnosis of gastritis by means of gastroscopy.

During this period, two innovations in the diagnosis of stomach lesions were introduced: in 1948, Benedict[5] invented gastroscopic biopsy under direct vision; and in 1949, Wood and his group invented blind gastric suction tube biopsy. These methods, by which actual living, functioning stomach mucosa could be gathered with no danger or morbidity to the patient, and prepared for histologic examination by the pathologist, eventually changed the entire concept of gastritis. In 1955 Ylvisaker *et al.*[45] reported 11 normal biopsies in 12 cases thought to be chronic hypertrophic gastritis at gastroscopy. Palmer[30] in 1954 found 42 normal biopsies out of 53 patients gastroscopically diagnosed as having chronic gastritis. After reviewing 1,213 patients at Walter Reed Army Hospital who had been both gastroscoped and biopsied, he concluded that the diagnosis of chronic hypertrophic gastritis had been made on normal stomachs. In 1956, Atkins and Benedict[1] studied 239 gastroscopic biopsies, then correlated the microscopic with the gastroscopic findings.

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They found that (a) in stomachs appearing normal to the gastroscopist 13 per cent had histologic gastritis; (b) cases thought gastroscopically to be chronic hypertrophic gastritis were associated with a normal histologic picture in most cases, and therefore such an appearance actually represents a normal variant; and (c) gastroscopic pictures of mixed acute and chronic gastritis showed microscopic correlation in but one third of the cases. They concluded, therefore, that gross gastroscopic appearances were not reliable in the diagnosis of gastritis. Joske *et al.*[20] studied 1,000 consecutive gastric biopsies; in 164 instances of normal gastric mucosa reported gastroscopically, they found histologically normal mucosa in only 87, and gastritis in the remander. Henning[19] in 1959 reported results on 3,000 suction biopsies, and concluded that gastroscopy in the diagnosis of chronic gastritis is useless. After 10 years of experience with this method, Mangold[26] also agrees that gastroscopy is not reliable in gastritis. Studies of other workers[4,37,38] confirm the above findings.

The concept that enlarged rugal folds as demonstrated roentgenographically represent gastritis has also been disproved by many. As early as 1947, Ricketts *et al.*[33] reported 4 cases of markedly enlarged rugae on first roentgenographic examinations, but which later showed normal appearance. They concluded that this phenomenon was due to spasm, not gastritis. Templeton[42] in his classic textbook on gastric roentgenology states, "in most cases of chronic hypertrophic gastritis the roentgenologic appearance is normal." Palmer[29] states that "no mucosal disease has a direct effect on general rugal size," and that "roentgenological study is not useful for detecting gastritis." Buckstein[7] considers that the roentgenographic diagnosis of gastritis is limited because (a) prominence of folds may be due to changes in the autonomic nervous system, and (b) changes in mucosa may be functional, for example, an allergy to food, rather than organic. He states that it is difficult to show an exact duplication of the mucosa because of mucus interference, varying of the barium solution, and technical difficulties. Stampfli[39] discusses and has demonstrated how the roentgenographic appearance of the gastric mucosa changes with position: the rugae appear shortened and tortuous when supine, less when prone; on standing, the rugae are stretched, close together and narrow. The appearance is also influenced by the degree of pressure, both intrinsic and extrinsic. Taft[41] in 1959 stated that "rugosity has no relation to inflammatory change", and "rugosity depends on the degree of contraction of the muscularis mucosae." He further stated that an increase in rugosity should not be construed as hypertrophic gastritis. Palmer[31] expressed the opinion that "chronic hypertrophic gastritis is a doubtful condition based on radiological findings only, and which cannot be confirmed clinically or pathologically; it is not a justifiable diagnosis." Authors of other articles and books concur with these opinions and findings.[25,32,40,44] Friedman[15] agreed and emphasized that a diagnosis of gastritis should be "deplored unless it has been confirmed by gastric biopsy." Buckstein[7] adds that the "roentgen diagnosis of gastritis is subject to considerable error", and that "prominent folds do not justify the diagnosis of hypertrophic gastritis."

Rarely, a carcinoma or a lymphosarcoma may present on the roentgenogram as giant enlarged folds.[13,28] It should be pointed out, however, that in these cases the appearance is due to actual large ridges in the tumor itself, and not to edema or to actual hypertrophy of the gastric rugae.[29]

There is another condition that does represent an actual hypertrophy of the mucosa—we shall call it "giant hypertrophy of the gastric mucosa" for reasons that will be discussed later, although various authors in the past have referred to the entity as "giant hypertrophic gastritis".[14,24] The condition was first described by Menetrier[2] in 1888. In this disease there is a striking enlargement of the rugae, resem-

bling the convolutions of the brain. The roentgenographic changes are so marked that if there is any doubt about the diagnosis, the disease is not present.[31] The changes can be generalized or localized, may or may not be associated with inflammatory reaction, and in some cases are associated with hypoproteinemia. It is the generalized type with protein abnormalities which is commonly referred to as Menetrier's disease. There are less than 100 such cases reported in the world literature. The localized type may occur in the gastric fundus or on the greater curvature;[8] although usually asymptomatic, it is of the utmost clinical importance because it so often will simulate a carcinomatous or lymphomatous tumor on roentgenograms.[21]

MATERIAL AND RESULTS

In an effort to correlate the clinical, gastroscopic, roentgenographic and pathologic findings of gastritis, a review was made of the records of all cases with such a diagnosis seen at the University of Illinois Research and Educational Hospitals in the last 5 years. Cases of acute gastritis were not used in the study because rarely had roentgenograms been taken in the course of the patients' illnesses. Furthermore, in these cases either the diagnosis was made on clinical grounds only without any laboratory basis, or, as in many patients, the diagnosis was made at autopsy and probably represented incidental terminal findings without clinical importance. The cases of chronic gastritis were used for the study only if roentgenograms had been made and could be located for inspection, and preferably if gastroscopy and/or biopsy had also been performed. All microscopic studies were done on surgical biopsies or autopsy specimens; gastroscopic biopsies have never been done at our hospital. The records were located by reviewing the material found in the departments of medical records and of pathology. Roentgenograms could not be consulted primarily because our department has not offered the diagnosis of gastritis on any roentgenographic study in the last 5 years. If the roentgenograms were not available, the case was discarded from the study. Included in the discarded group were many cases in which a diagnosis of chronic gastritis was made only because no other condition could be found to account for the patient's symptoms, roentgenographic and other studies being negative. Of the nearly 200 records reviewed by the author, 50 cases met the above criteria and are presented in this paper.

CORRELATION BETWEEN ROENTGENOGRAPHY AND GASTROSCOPY

Table 1 shows patients who had both roentgenographic and gastroscopic studies, and indicates the lack of correlation between the 2 methods. Of 15 cases, 9 demonstrated normal rugae on roentgenograms, yet were diagnosed by the gastroscopist as chronic atrophic (Fig. 1), chronic hypertrophic (Fig. 2), or superficial gastritis. In Case 4, roentgenograms showed polypoid thickening of mucosa, but gastroscopy revealed atrophic gastritis. In Cases 14 and 15 (Fig. 3), roentgenograms showed thickened mucosa; gastroscopy was normal. There were only 2 cases showing agreement between the 2 methods, both demonstrating thickened folds on roentgenograms and hypertrophic gastritis on gastroscopy. In Case 13, roentgenograms revealed a small antral ulcer with normal rugae. Gastroscopy showed a suspicious nodular area in the antrum. Biopsy revealed a normal stomach without mucosal thickening or ulcer. No biopsies were done in the other cases.

CORRELATION BETWEEN ROENTGENOGRAPHY AND PATHOLOGY

Table 11 shows a comparison between the roentgenographic and the pathologic findings, most of which were on surgical biopsies. There were 19 upper gastrointestinal series showing normal gastric rugae; all showed chronic gastritis on biopsy (Fig. 4 and 5). Two cases, No. 18 and 40, showed narrowing and rigidity of the distal esophagus, suggesting the diagnosis of esophagitis;

TABLE I

COMPARISON OF ROENTGENOGRAPHIC AND GASTROSCOPIC FINDINGS

Case	Roentgenography	Gastroscopy	Biopsy
1. F.B.	Normal rugae	Chronic superficial gastritis	None
2. L.L.	Normal rugae	Atrophic gastritis	None
3. H.K.	Normal rugae	Atrophic gastritis	None
4. C.R.	Polypoid thickening of rugae	Atrophic gastritis	None
5. E.D.	Normal rugae	Atrophic gastritis	None
6. R.H.	Normal rugae	Chronic hypertrophic gastritis	None
7. A.B.	Thick, tortuous folds	Hypertrophic gastritis	None
8. C.M.	Normal rugae	Chronic hypertrophic gastritis	None
9. J.O'D.	Thick, tortuous folds	Chronic hypertrophic gastritis	None
10. C.S.	Normal rugae	Hypertrophic gastritis	None
11. M.L.	Normal rugae	Chronic hypertrophic gastritis	None
12. D.M.	Normal rugae	Chronic hypertrophic and atrophic gastritis	None
13. S.S.	Normal rugae	Suspicious nodular area in antrum	Normal stomach
14. R.J.	Thickened folds	Normal	None
15. H.S.	Thickened folds	Normal	None



FIG. 1. Case 3, H.H.K. Normal mucosal folds were reported on roentgenograms of this 43 year old male. Gastroscopy showed atrophic gastritis. No biopsy was done.

biopsies of these exact areas in both cases revealed chronic gastritis. There were only 2 cases, No. 20 and 42, of true chronic gastritis which showed prominent folds on the roentgenograms and it should be noted that both also had duodenal disease. There were 4 cases of antral narrowing and irregularity, 3 of which showed chronic gastritis; the fourth was normal (Fig. 6). One case, No. 38, was diagnosed as adult hypertro

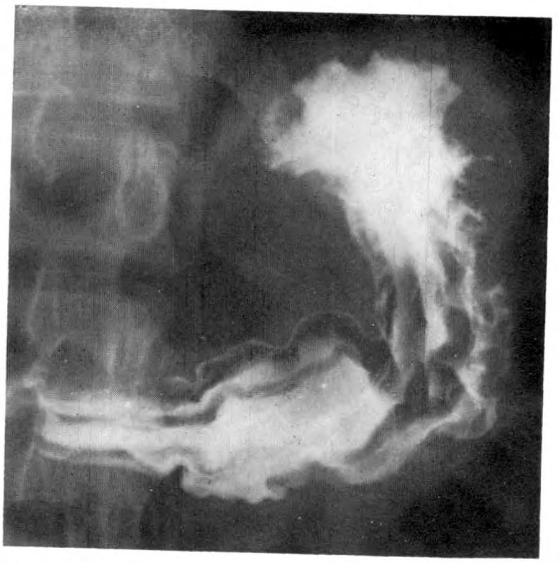


FIG. 2. Case 10, C.S. This 35 year old male presented with substernal pain. A gastrointestinal series was normal. Gastroscopy revealed hypertrophic gastritis. The patient was discharged with this diagnosis. There was no biopsy.

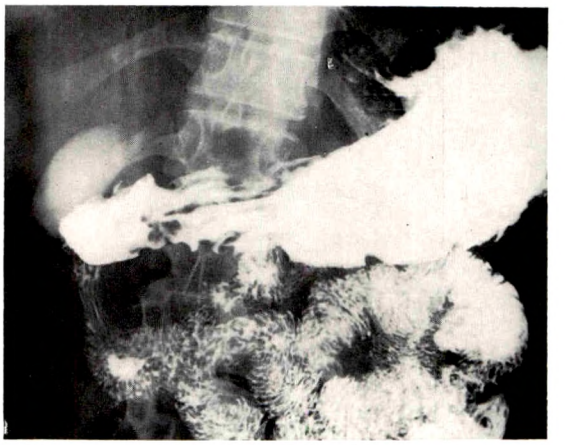


Fig. 3. Case 15, H.S. This 46 year old female presented with vague epigastric distress. Roentgenograms revealed rather marked thickening and tortuosity of gastric rugae. Gastroscopy revealed a normal stomach. There was no biopsy.

phic pyloric stenosis roentgenographically and biopsy proved this to be correct.

Cases of Tumor-Simulating Giant Hypertrophy of the Gastric Mucosa

Table III lists the patients whose roentgenograms simulated tumors, and whose biopsies showed various types of chronic gastritis. For reasons which will become apparent later, the author has classified these cases as giant hypertrophy of the

Table II

Comparison of Roentgenographic and Biopsy Findings

Case	Roentgenography	Biopsy
16. J.M.	Duodenal ulcer and normal rugae	Chronic gastritis
17. P.C.	Functioning gastroenterostomy with normal rugae; possible marginal ulcer	Subacute gastrojejunitis with jejunal ulcer
18. N.G.	Esophagogastric narrowing	Chronic gastritis (tissue from lower esophagus)
19. J.F.	Narrowing of antrum and prolapse of antral mucosa	Mild chronic antral gastritis
20. O.M.	Thickened folds and deformed bulb	Chronic gastritis and duodenitis
21. H.E.	Normal rugae	Mild chronic gastritis
22. A.F.	Normal rugae	Mild chronic gastritis
23. I.J.	Gastric ulcer with normal rugae	Ulcer with chronic granulomatous gastritis, etiology unknown
24. M.W.	Gastric ulcer with normal rugae	Mild chronic gastritis
25. H.M.	Normal rugae	Mild chronic gastritis
26. H.S.	Antral narrowing	Chronic gastritis
27. J.S.	Normal rugae	Chronic gastritis
28. R.C.	Normal rugae	Chronic gastritis
29. J.L.	Normal rugae	Subacute gastritis
30. F.D.	Normal rugae	Chronic gastritis
31. M.P.	Normal rugae	Chronic gastritis
32. C.S.	Narrowing of antrum with ulcer	Subacute gastritis with ulcer
33. L.K.	Normal rugae	Chronic gastritis
34. B.S.	Normal rugae	Subacute gastritis
35. A.K.	Normal rugae	Chronic gastritis
36. L.C.	Normal rugae	Hypertrophic gastritis
37. N.L.	Normal rugae	Chronic gastritis
38. V.H.	Hypertrophy of pyloric muscle, adult type	Hypertrophy of pyloric muscle
39. C.J.	Normal rugae	Chronic gastritis
40. G.D.	Narrowing of lower esophagus	Chronic gastritis (tissue from lower esophagus)
41. L.C.	Normal rugae	Chronic gastritis
42. J.G.	Duodenal ulcer with very prominent gastric rugae	Duodenal ulcer and chronic gastritis
43. C.B.	Antral narrowing and irregularity	Normal stomach

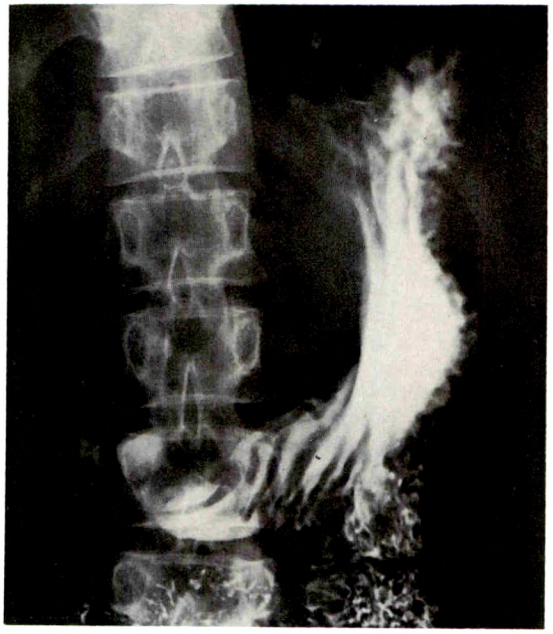


Fig. 4. Case 17, P.C. Roentgenograms showed a normal mucosa in both the stomach and gastroenterostomy anastomosis site in this female patient. A marginal ulcer was questioned. Surgery and biopsy revealed a jejunal ulcer with a gastrojejunitis.

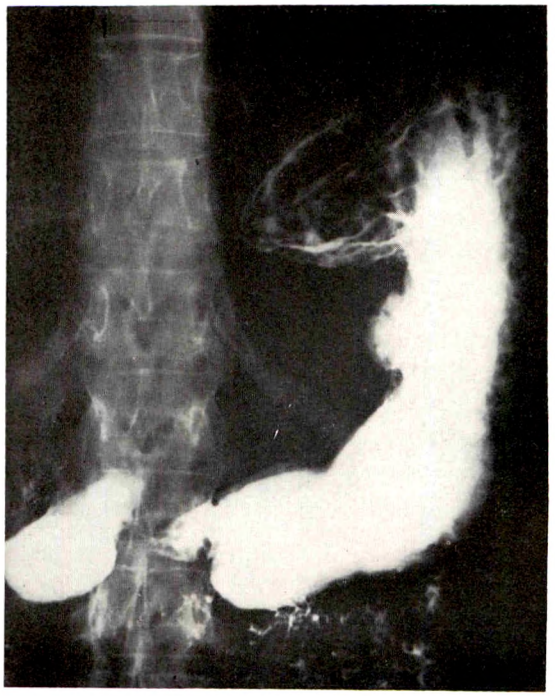


Fig. 5. Case 24, M.W. This 42 year old female showed roentgenographic findings of gastric ulcer and normal mucosal folds. Biopsy revealed a benign ulcer with chronic gastritis in the remainder of stomach. There was no gastroscopy.

gastric mucosa. In 5 of the 7 patients, the chronic gastritis changes were localized and simulated a gastric neoplasm (Fig. 7). In 2 cases, generalized hypertrophic folds were present. Case 50 (Fig. 8) was associated with hypoproteinemia, and represents a classic Menetrier's syndrome.

Table IV shows a summary of the findings regarding the accuracy of roentgenology and gastroscopy in the diagnosis of gastritis. There was an 87 per cent disagreement between roentgenographic and gastroscopic studies in the interpretation of the appearance of the gastric mucosa. When compared to the pathologic evidence of chronic gastritis in the body of the stomach, roentgenograms were only 10 per cent accurate.

It is interesting to note that roentgenology was found to be 80 per cent accurate in detecting lesions of the gastric antrum. This accuracy rate refers only to the differentiation between a normal and an abnormal gastric antrum, and in no way reflects the degree of accuracy in differentiating a benign inflammatory process from a malignant neoplasm. This presents a different problem than the one discussed here, and for such a discussion the reader is referred

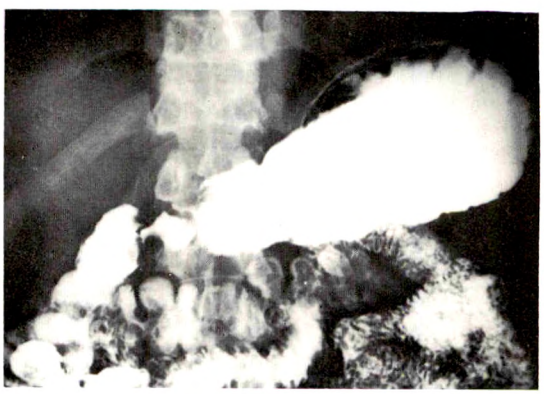


Fig. 6. Case 43, C.B. In this 71 year old male an upper gastrointestinal series showed marked deformity of the antrum with irregular and thickened mucosal folds in the area. A diagnosis of severe antral gastritis was made. Gastroscopy was normal. Autopsy following sudden cardiac death showed a completely normal stomach.



Fig. 7. Case 46, L.S. Roentgenograms revealed an irregular filling defect high on the lesser curvature in this male patient. Biopsy revealed chronic hypertrophic gastritis.

Table IV

SUMMARY OF ACCURACY OF METHODS

Method	No. of Cases	Per Cent Agreement	Per Cent Disagreement
Roentgenography vs. Gastroscopy	15	13	87
Roentgenography vs. Pathology (excluding antral and esophageal lesions)	21	10	90
Roentgenography vs. Pathology (antral lesions only)	5	80	20

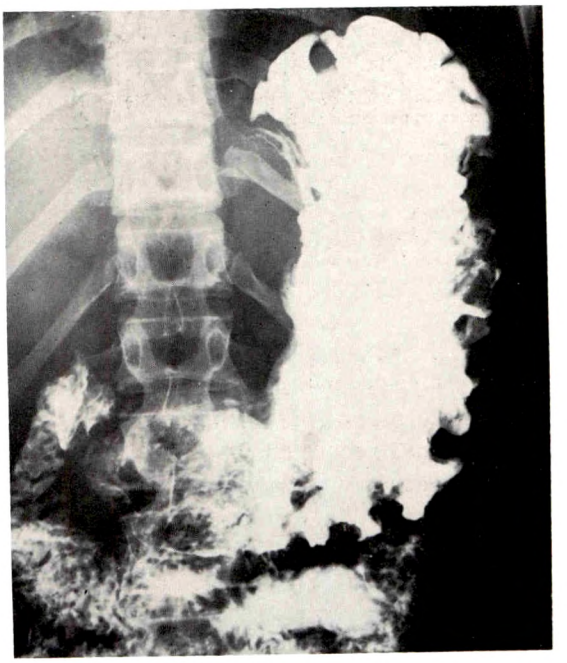


Fig. 8. Case 50, S.R. This 18 year old female showed giant hypertrophy of the gastric mucosa associated with chronic gastritis and hypoproteinemia (Menetrier's syndrome). Notice the enormous size of the mucosal folds, even upon distention of the stomach with a large amount of barium.

Table III

GIANT HYPERTROPHY OF GASTRIC MUCOSA SIMULATING TUMORS

Case	Roentgenography	Biopsy
44. E.C.	Pyloric ulcer with mass	Pyloric ulcer with chronic perigastric inflammation
45. B.N.	Mass in cardia, probably carcinoma	Autopsy: subacute necrotizing gastritis
46. L.S.	Tumor of fundus	Chronic hypertrophic gastritis
47. J.M.	Ulcerating tumor of antrum	Chronic gastritis
48. J.T.	Malignant appearing mass in antrum	Perigastric inflammation
49. L.G.	Inadequate roentgen study (gastroscopy revealed chronic hypertrophic gastritis)	Autopsy: extensive generalized giant hypertrophic gastritis
50. S.R.	Extensive generalized thickening of gastric rugae	Extensive generalized giant hypertrophic gastritis

elsewhere.[6] We are dealing here with gastritis in the body and fundus of the stomach, and therefore no further mention of similar lesions in either the gastric antrum or the lower esophagus will be made.

DISCUSSION

The results of this study bear out what so many other workers have already observed—that neither roentgenology nor gastroscopy is reliable in the diagnosis of gastritis.

CLINICAL SIGNIFICANCE OF GASTRITIS

Mention should also be made concerning the serious doubt regarding the clinical significance of gastritis that has been raised in the literature. Gastrointestinal symptoms are difficult to judge. Such complaints as abdominal pain, nausea, and flatulence are nonspecific and most difficult to evaluate. Since gastric ulcers and carcinomas are associated with a very high incidence of coexistent gastritis,[25] how can one attribute the patient's symptoms to gastritis rather than to the primary disease? After partial gastrectomy, there frequently remains a chronic nonprogressive gastritis,[25] but certainly most of these patients never experience definite symptoms. The incidence of microscopic gastritis in normal, asymptomatic people is high. Hebbel[17] in a study of 97 autopsies on patients who had never had gastrointestinal symptoms, found 72 per cent with evidence of gastritic changes. Mangold[26] stated, "symptoms suggestive of gastritis should be interpreted with great caution." Heinkel[18] also doubted that any definite symptoms can be correlated with gastritis. Larson and Kling[23] discussed the doubt that exists regarding the significance of gastritis even in the minds of the pathologists. The present status regarding this point can be summed up by Coghill[10] who feels that "there is no convincing evidence that chronic gastritis has any clinical significance."

GIANT HYPERTROPHY OF THE GASTRIC MUCOSA

From the vast literature about gastritis, there has emerged one important, definite and most significant entity, that of giant hypertrophy of the gastric mucosa, or, as it is sometimes called, giant hypertrophic gastritis. This has been referred to above. It is felt that the former name is much preferred because recent evidence suggests that the pathologic changes in this disease are basically neoplastic, perhaps an anatomic variant of gastric adenomatosis, and that inflammatory reaction is a secondary occurrence.[34,44] Therefore, it seems that only more confusion is added to an already complicated subject if the word gastritis is tagged onto this entity. Certainly its importance is related to its differential diagnosis from a malignancy in cases of the local type, and to the severe systemic illness and protein imbalance in the generalized forms; that there may be a few inflammatory cells present on the microscopic sections is probably of very little importance.[40] Although the status of this condition as a precursor to carcinoma is not definitely clear,[16] there is probably no relationship.[9] As shown in our study, both roentgenology and gastroscopy are of value in establishing the diagnosis.[22] However, to definitely differentiate either the localized or the generalized form of the disease from a malignancy requires a biopsy.

How, then, should the radiologist interpret a roentgenogram when he is confronted with thickened gastric folds? He perhaps should mention the fact, just as he would if he saw an azygous lobe, an accessory ossification center, or a spina bifida occulta. However, in his conclusion he has no other choice but to consider the roentgenogram normal. Since gastritis occurs just as commonly in persons who exhibit normal mucosal folds on roentgenograms as in persons with enlarged folds, it would be unwise for the radiologist to diagnose gastritis only in the latter group. If on the other hand the radiologist is confronted with giant enlargement of the folds which cannot be stretched with overdistention by barium or with pressure exerted by the examining hand, one must consider generalized hypertrophy of the gastric mucosa, or an infiltrative type of carcinoma or lymphoma.

If he discovers a localized filling defect type of lesion within the stomach, he should always think of the possibility of localized giant hypertrophy.

CONCLUSIONS AND SUMMARY

1. Gastritis microscopically is present quite frequently in clinically normal patients. It is invariably present in conjunction with such conditions as gastric ulcer and carcinoma, and subtotal gastrectomy. Therefore, the clinical significance of this entity is doubtful, and thus far no convincing evidence of its importance has been established.

2. A review of gastritis cases at the University of Illinois Research and Educational Hospitals in the past 5 years, along with an extensive review of the current literature on the subject, indicates that roentgenology and gastroscopy are totally inadequate and completely unreliable in establishing the diagnosis of gastritis. These two methods can be correlated neither with each other nor with the actual pathology, in regard to gastritis.

3. The entity of giant hypertrophy of the gastric mucosa is reviewed and its importance is emphasized. The terms of chronic or giant hypertrophic gastritis should not be used, since the condition is primarily neoplastic, not inflammatory. The localized type is clinically unimportant, except for its difficult differentiation from a malignancy. The generalized form can be associated with marked systemic signs and symptoms (Menetrier's syndrome) and in some cases may simulate a carcinoma or lymphoma.

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ENTEROGASTRIC REGURGITATION DURING BARIUM ENEMA EXAMINATION

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IT IS generally assumed that barium appearing in the stomach in the course of a barium enema examination reaches the gastric level by way of an abnormal short circuit or fistulous tract. This assumption is corroborated by all that has appeared in the literature.[2,3,7,9] Paul and Juhl[7] in a recently published textbook on roentgen interpretation indicate that if a previous surgical procedure, *i.e.*, gastroenterostomy, has not been done, a diagnosis of carcinomatous invasion and necrosis either in the stomach or transverse colon is justified. It is usually considered unlikely that colonic barium ever reaches the stomach through the small bowel under normal circumstances.[4,6,9]

It is the purpose of this report to present 2 cases in which barium has extended to the stomach during a barium enema procedure. In one case, a gastrocolic fistula was roentgenographically identified and proven at surgery. In the second and more interesting case, colonic barium reached the stomach without demonstrable fistula or evidence of short circuiting of the gastrointestinal tract. In this case, surgical proof is lacking since the patient never had sufficient symptoms to warrant laparotomy. In defense of the impression of enterogastric reflux without fistula, the roentgenograms in this case have been reviewed independently by several prominent radiologists[5,4,6] and all agree that the barium seen in the stomach extended from the colon by virtue of an unusual degree of regurgitation into the small bowel.

REPORT OF CASES

CASE I. W.S., a 72 year old well nourished white female, was admitted to the hospital on November 5, 1961, with acute right upper abdominal pain, nausea and vomiting. There was constipation early during her hospital stay but severe diarrhea developed within a few days. There was no previous surgery and symptoms came on abruptly about 2 days prior to admission. The clinical impression was that of an acute cholecystitis. A cholecystogram revealed, in addition to a nonfunctioning gallbladder, evidence of air outlining the hepatic and common ducts (Fig. 1). A barium enema study disclosed a fistula between the gallbladder, hepatic flexure and stomach (Fig. 2 and 3). At surgery, a cholecystectomy and resection of the fistula were accomplished and the patient has had a complete and uneventful recovery.

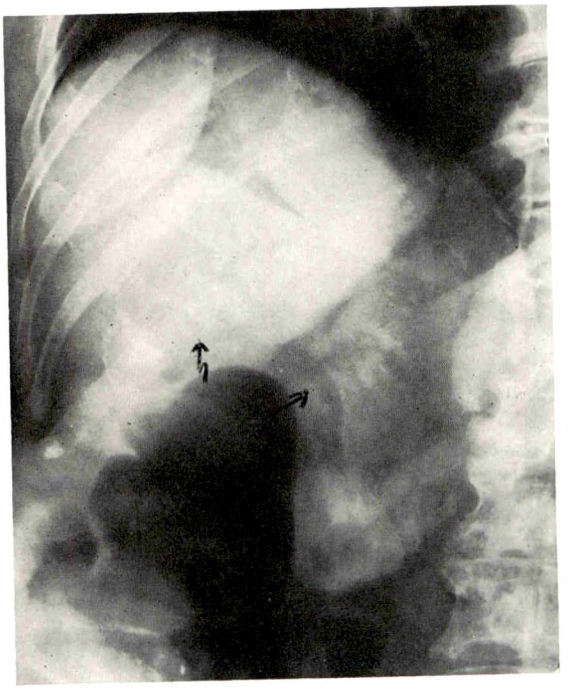


FIG. 1. Cholecystogram showing nonfunctioning gallbladder and air filling bile duct system.

CASE II. R.C.H., a well nourished, well developed, white female, was referred to the X-ray Department on December 12, 1960, as an outpatient for a routine examination of her colon because of vague lower abdominal pain. There was no history of constipation or diarrhea. There was no weight loss and no symp-

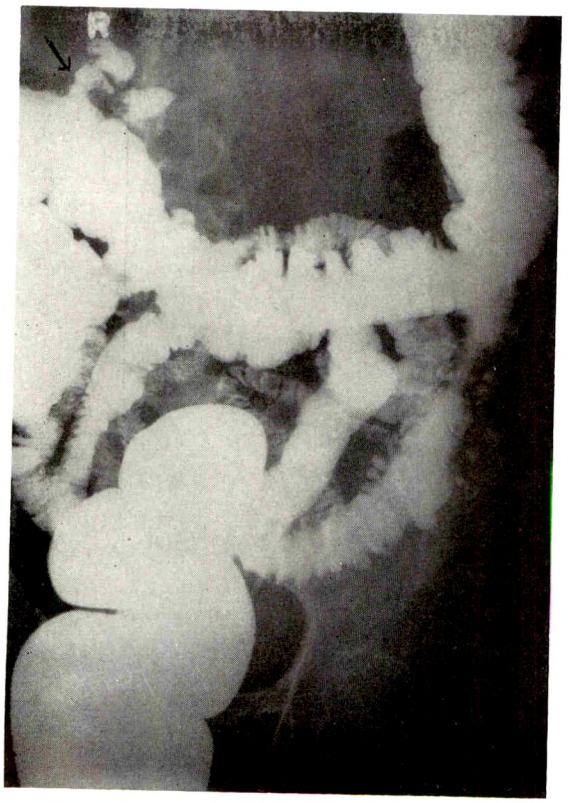


Fig. 2. Pre-evacuation barium enema study showing fistula with gallbladder.



Fig. 3. Post-evacuation barium enema study showing gallbladder and gastrocolic fistula.

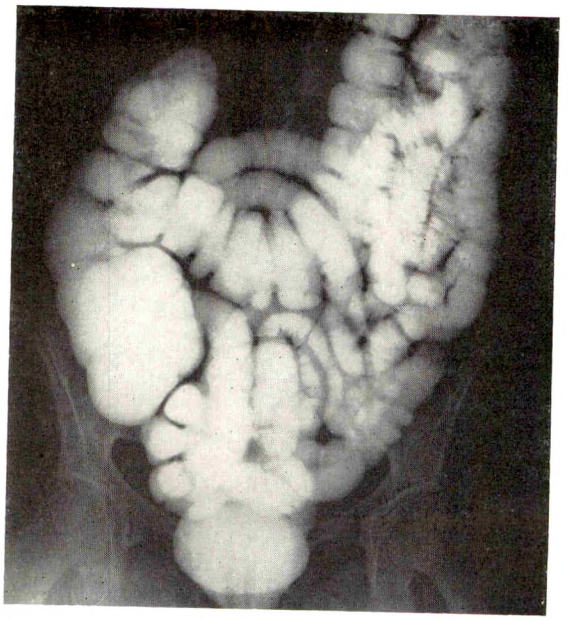


Fig. 4. Pre-evacuation barium enema study showing normal colon with extensive small bowel regurgitation.

toms related to the upper gastrointestinal tract. The clinical impression was that of an irritable colon and a barium enema examination was ordered to rule out organic disease. Fluoroscopically, the colon filled readily to the cecum with free regurgitation occurring into the terminal ileum. Approximately one and a half quarts of barium mixture was administered to complete the examination. The bowel had a normal caliber, the haustral markings were preserved and aside from an incompetent ileocecal valve, organic disease was not demonstrated. A pre-evacuation roentgenogram (Fig. 4) showed marked small bowel filling without evidence of barium in the stomach. The barium was evacuated promptly without difficulty, the patient experiencing no nausea or vomiting and, as usual, nothing was taken orally. The post-evacuation roentgenograms (Fig. 5 and 6) revealed barium in the stomach and duodenal bulb, confirmed by repeat fluoroscopy. One week later, a stomach and small bowel study was done and no abnormalities found. The colon examination was repeated 2 months later and on this occasion 2 quarts of barium mixture (2,000 cc.) was used and though similar small bowel regurgitation was seen, with jejunal filling, gastric reflux failed to occur (Fig. 7 and 8). The past history

revealed that a cholecystectomy and appendectomy were done elsewhere on November 16, 1955. Exploration of the abdomen at that time disclosed no abnormalities aside from the cholecystitis with stones and a chronic appendicitis. There was no evidence of any etiologic agent which might cause a fistula between the stomach and bowel.



Fig. 6. One hour delayed post-evacuation barium enema examination confirming gastric filling.

COMMENT

Reflux filling of the small bowel during barium enema procedure depends on the competency of the ileocecal valve. Buckstein[1] in his monograph on functional disorders of the large intestine devotes considerable discussion to ileocecal valve competency and its significance. He states "Ileocecal regurgitation plays an important part in the literature of colonic disorders. A remarkable observation was made by Grutzner, quoted by Pavlow, who found that particles of hair, charcoal and unboiled starch injected into the lower bowel with a saline enema might make their way into the small intestine and even into the stomach. These observations were confirmed by Sabbatini, Fasola and Cannon using the roentgen-ray method, after a barium enema." This experimental observation of material

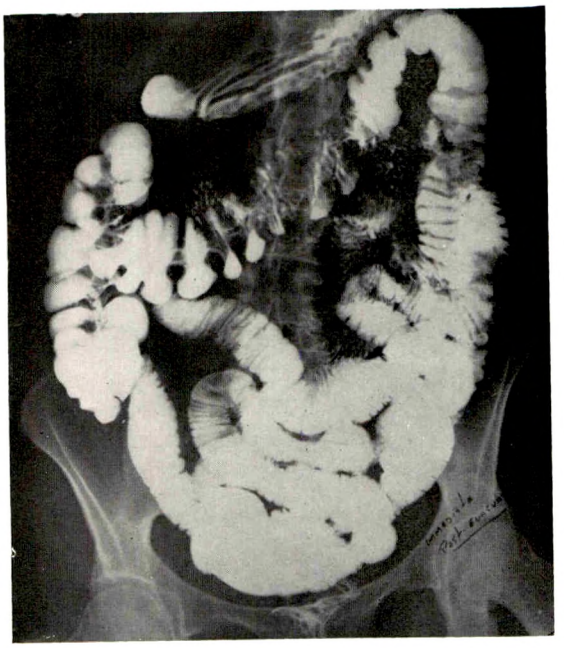


Fig. 5. Immediate post-evacuation barium enema examination showing gastric regurgitation.



Fig. 7. Pre-evacuation barium enema (repeat examination) showing again extensive small bowel reflux.

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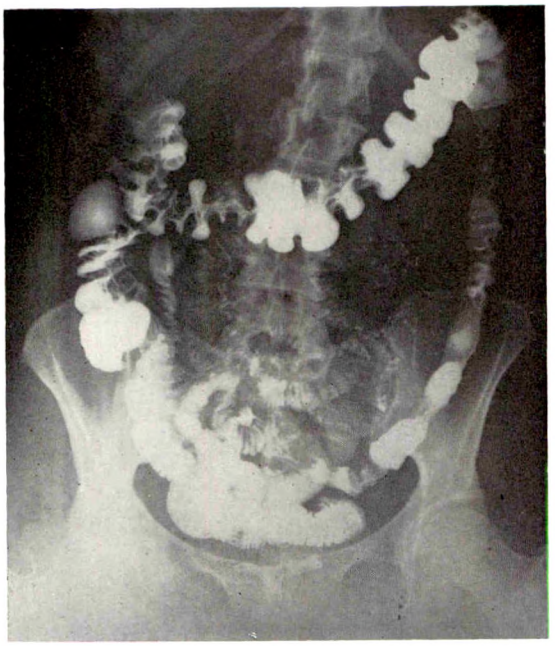


Fig. 8. Immediate post-evacuation barium enema (repeat examination) demonstrates no gastric reflux. The delayed post-evacuation roentgenogram showed similar findings.

reaching the stomach from the colon appears to be the only reference found in the literature. Gianturco[4] states that he has on occasion deliberately attempted to produce reflux into the stomach during a barium enema procedure using a large quantity of barium mixture but has not been able to accomplish it. It is the author's opinion that a combination of ileocecal valve incompetency and some degree of reverse peristalsis of the small intestines is required to bring about sufficient back flow of barium to reach the gastric level. The amount of barium used may be irrelevant. On this point, it is suggested that whenever unusual regurgitation into the small bowel occurs, a 1 or 2 hour delayed evacuation roentgenogram may at times reveal the surprising fact that barium has reached the stomach. Obviously, it is an extremely rare occurrence. One need only speculate on what effects colonic content contaminating the normally sterile upper gastrointestinal tract might have on normal intestinal physiology. Ascending cholangitis would likely be much more prevalent should such contamination occur very frequently. In the case presented here, it is unfortunate that surgical confirmation is lacking. Nevertheless, most patients with gastrointestinal fistula are seriously ill. These patients usually demonstrate some degree of interference with normal nutrition. Weight loss, anemia, diarrhea, nausea and vomiting are all prominent symptoms. History of previous surgery is important since the breakdown of a marginal ulcer in the stoma of a gastroenterostomy is the most frequent cause of gastrocolic fistula.[7] It must be reiterated that the patient presented in this report is well nourished, essentially asymptomatic and remains alive and well today. In the absence of surgical proof, it must be concluded that this is, in fact, a case of enterogastric regurgitation occurring during barium enema examination in a normal patient.

Conclusion

Enterogastric reflux during barium enema examination usually denotes the presence of a fistula or short circuiting in the gastrointestinal tract. A case of enterogastric regurgitation during barium enema study in a patient showing no clinical or roentgenographic evidence of a fistula is presented. Ileocecal valve incompetency and reverse small bowel peristalsis are given as the most likely explanation for this unusual occurrence. By contrast, a case of gastrocolic fistula is also presented. The barium enema examination, a common roentgenographic procedure, is not entirely without hazard.[2,8] The fact that, on occasion, colonic barium may reflux to the stomach is an additional potential hazard to normal gastrointestinal physiology. Review of the literature confirms the rarity of this phenomenon.

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I would like to acknowledge my gratitude to Doctors J. D. Hull, H. A. Hindman and G. S. Lietz for their aid in obtaining the historical background of the cases presented in this paper.

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DUODENAL ANOMALIES IN THE ADULT*

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THE great majority of duodenal anomalies cause intestinal obstruction early in life and are diagnosed in infancy or childhood. In some instances, however, the physical characteristics of the anomaly are such that recognition is delayed until adult life. The anomaly may be intrinsic to the duodenum or may be related to adjacent structures. An awareness of the clinical and roentgenographic features of these anomalies should enhance the probability of correct preoperative diagnosis.

EMBRYOLOGY

The duodenum undergoes three distinct embryologic phases; namely, rotation, fixation and vacuolization. Arrest or delay of these phases is responsible for most duodenal anomalies. Abnormalities in the development of the pancreas and mesentery account for the remainder.

Rotation. At the eighth week of fetal life, the midgut lies within the umbilical sac, its mesentery occupying the sagittal plane. At this point, the gut rotates 90° in a counterclockwise direction, the mesentery now assuming the horizontal plane. At the tenth week, the midgut returns to the peritoneal cavity. There follows rapidly a counterclockwise rotation of 180° around the superior mesenteric axis, bringing the third portion of the duodenum into the narrow angle between the superior mesenteric artery and the aorta.[19,29,31,47,69]

Fixation. The dorsal mesentery, coming into contact with the posterior peritoneum, agglutinates, allowing fixation of the duodenum in this position. At the same time the ventral mesentery becomes obliterated. Failure of agglutination of the dorsal mesentery results in anomalies of duodenal mobility. Failure of the ventral mesentery to obliterate results in the formation of abnormal bands and membranes.

Vacuolization. At about the sixth week of intrauterine life, the epithelium of the duodenum begins to proliferate and rapidly occludes the lumen. Shortly thereafter, two rows of vacuoles appear. These vacuoles coalesce rapidly and the lumen is re-established by the tenth fetal week. Failure of coalescence results in stenoses and septa.[55,59] Retention and isolation of vacuoles may be responsible for duodenal reduplications.[67]

Development of the Pancreas. The pancreas forms from the coalition of a large dorsal anlage with a smaller ventral anlage which is attached to the second portion of the duodenum. If, during rotation of the duodenum, the ventral anlage is not brought into direct contact with the dorsal anlage, the second portion of the duodenum may become "sandwiched" between them, resulting in an annular pancreas. When multiple pancreatic anlagen are present, as is often the case, one or more of these may be misplaced, resulting in aberrant pancreatic foci.[2]

MATERIAL AND METHODS

In the 15 year period between 1945–1960, 26 adults with proven congenital duodenal anomalies were seen at the New York Hospital—Cornell Medical Center. This total does not include cases of duodenal malposition, which were rarely proven. Of the total of 26, only 14 had symptoms related to the anomalies. Many of the nonsymptomatic cases represented small foci of aberrant pancreas incidentally discovered at autopsy.

Of the symptomatic cases, 4 were aberrant pancreas, 3 were arteriomesenteric occlusions, 3 were annular pancreas and one each was reduplication cyst, aberrant vessel, cholecystoduodenocolic band and hereditary megaduodenum. An analysis of the 26 cases is presented in Tables I and II.

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Table I

PROVEN CASES OF CONGENITAL LESIONS OF THE DUODENUM IN THE ADULT AT THE NEW YORK HOSPITAL: JUNE, 1945 THROUGH JUNE, 1960*

Type of Cases	No. of Cases	Positive Roentgenographic Findings	Negative Roentgenographic Findings	Roentgenographic Study Not Performed
I. Symptomatic, Surgically Proven Cases (See Table II for analysis of these cases)	14	12	2	0
II. Asymptomatic, Incidentally Discovered Cases at Surgery or Autopsy	12	—	6	6
a. annular pancreas	1	—	1	—
b. aberrant pancreas	10	—	4	6
c. cholecystoduodenocolic band	1	—	1	—
Total I and II	26	12	8	6

* Cases of duodenal inversion or malrotation are not included.

Table II

CASES OF SYMPTOMATIC, SURGICALLY PROVEN CONGENITAL LESIONS OF THE DUODENUM IN THE ADULT AT THE NEW YORK HOSPITAL: JUNE, 1945 THROUGH JUNE, 1960

Lesion	No. of Cases	Age and Sex	Positive Roentgenographic Findings	Negative Roentgenographic Findings
duplication cyst	1	48F	1	—
aberrant vessel	1	31M	1	—
annular pancreas	3	59M, 64M, 66F	3	—
cholecystoduodenocolic band	1	38M	1	—
aberrant pancreas	4	43M, 50F, 55F, 64M	2	2*
superior mesenteric artery obstruction	3	13M, 47M, 47F	3	—
megaduodenum	1	21M	1	—
Total	14	9 Males 5 Females	12	2

* Filling defect of aberrant pancreas not seen but associated duodenal lesion evident; in one case duodenal ulcer, in other deformed duodenal bulb with pseudodiverticulum.

For the purpose of this study, the age of 13 years was selected as the dividing line between childhood and adulthood. This is in keeping with the policies of The New York Hospital.

ARTERIOMESENTERIC OCCLUSION OF THE DUODENUM

Obstruction of the third portion of the duodenum by the superior mesenteric artery and its enveloping mesentery has been recognized for centuries. It has been referred to as duodenal ileus,[1] chronic duodenal dilatation,[19] duodenal stasis,[21] mesenteric vascular compression,[66] gastromesenteric ileus,[68] megaduodenum,[70] arteriomesenteric ileus,[45] and superior mesenteric artery syndrome.

Etiologic Factors. The mechanism by which the third portion of the duodenum becomes wedged in the angle made by the superior mesenteric artery and aorta has been discussed. Any factor which increases the "drag" of the mesentery will decrease this angle and will enhance the likelihood of duodenal compression.[16] Visceroptosis is the most commonly associated condition.[21,32] Rapid change in body weight may be an occasional cause.[20,21] Less commonly associated factors are congenitally short mesentery,[19] surgically shortened mesentery,[32] aberrant branches of the superior mesenteric artery,[20,21] multiple pregnancies,[32] and hyperextension of the spine.[66]

Incidence. This entity is probably far less common than previously believed. Many of the cases described prior to 1940 undoubtedly were due to such factors as postoperative electrolyte imbalance, hereditary megaduodenum and inflammatory or neoplastic obstructions. At least one author[18] persuasively questions the very existence of this syndrome. Most authorities believe it to be a rare but definite entity. The incidence at autopsy has been reported as 0.6 per cent in 4,500 examinations and 0.2 per cent in 30,000 examinations. In 1,500 consecutive barium examinations of the upper gastrointestinal tract, the incidence was 0.3 per cent.[32]

Age and Sex. Females predominate by approximately 3 to 1. The diagnosis is rarely made before the age of 5 years. Most reported cases were diagnosed between ages 15 and 50.

Clinical Features. Symptoms usually date from childhood, though on occasion may be rather acute. The most characteristic symptoms are postprandial fullness and epigastric pain, relieved by assuming the knee-elbow or prone position. This position reduces the "drag" of the mesentery. Vomiting is uncommon. Borborygmi, heartburn and constipation are fairly common complaints.

Roentgen Findings. Upright fluoroscopy is essential. The duodenum is dilated up to a point just to the left of the spine. At this site there is a sharp cut-off. Marked to-and-fro churning of the barium may be noted. In most cases, the stasis is partially alleviated by placing the patient in the prone position. The same relief may be observed in the upright position if the examiner applies firm upward pressure on the lower abdomen (Hayes' maneuver).[25] On follow-up roentgenograms, barium may be retained in the duodenum for as long as 48 hours.

The differential diagnosis includes anomalous bands, adhesions, hereditary megaduodenum, duodenal neoplasms and extrinsic masses.

ILLUSTRATIVE CASES

Case 1 (Fig. 1). E.B., a 47 year old white male, entered The New York Hospital on October 19, 1956 with a history of anorexia and a 35 pound weight loss. The weight loss had taken place over a period of 2 years. The patient had suffered from dyspnea, cough and repeated pneumonias for many years. There was no family history of gastrointestinal difficulties.

On physical examination the patient weighed only 108 pounds. There was evidence of marked emphysema. Laboratory findings were normal, except for a hemoglobin of 17.6 gm. per 100 cc. (gm. per cent).

Roentgen study of the upper gastrointestinal tract revealed a normal esophagus and stomach.

The duodenum was markedly dilated as far as the distal third portion. The obstruction was complete for $3\frac{1}{2}$ hours, after which the barium meal was noted to trickle past the obstructed point. The roentgen interpretation was that of a primary duodenal neoplasm or extrinsic invasion from a pancreatic tumor.

At laparotomy, the duodenum was uniformly dilated to a diameter of 3 inches. The superior mesenteric artery compressed the duodenum at the point of obstruction. A duodenojejunostomy was performed. The postoperative course was uneventful, and the patient has done well.

Case II (Fig. 2). R.C., a 13 year old white male, was admitted to The New York Hospital on August 24, 1957 complaining of abdominal pain. This pain had occurred sporadically since the age of 13 months. The pain was postprandial and was accompanied by abdominal distention. Relief could be obtained by eructation or by passage of flatus. The attacks had become progressively more frequent, occurring approximately 8 times a month at the time of admission. Prior to admission, a right upper quadrant mass was palpated on a number of occasions, being present only during the attacks.

Physical examination and laboratory studies were normal.

An upper gastrointestinal study revealed moderate dilatation of the first, second and third portions of the duodenum. There was exaggerated gastric peristalsis; reversed duodenal peristalsis was also noted. Barium trickled slowly into the jejunum.

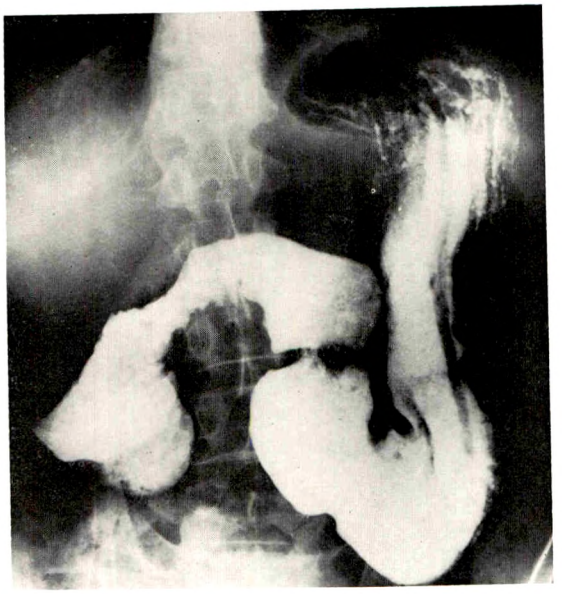


Fig. 1. Case I. Arteriomesenteric occlusion of the duodenum. Duodenum markedly dilated.

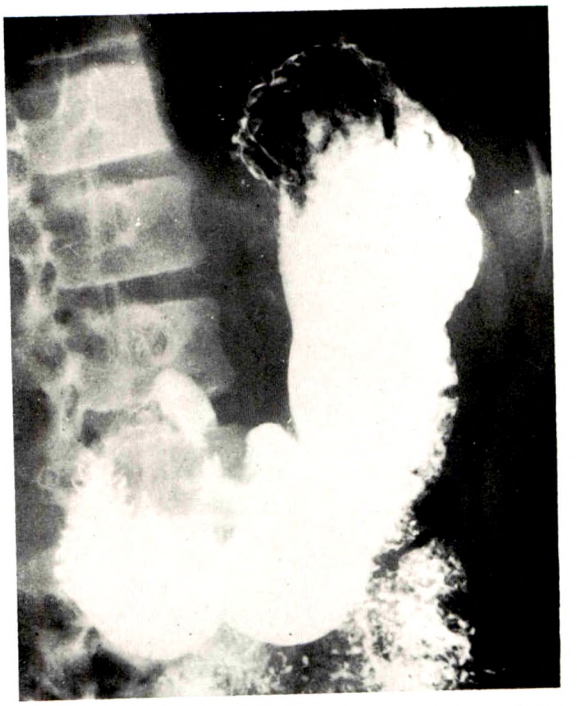


Fig. 2. Case II. Arteriomesenteric occlusion of the duodenum. Marked dilatation of second and third portions.

At laparotomy the duodenum was dilated to the point at which the superior mesenteric artery crossed it. A duodenojejunostomy was performed. A gastrointestinal study 2 months following discharge showed a normally functioning duodenojejunostomy. One year following surgery the patient was asymptomatic.

DUODENAL INVERSION

Variations in the course of the duodenum are related to abnormalities in the length and fixation of the primitive dorsal mesentery. Anomalous fixation of the pancreas, right kidney, transverse mesocolon and portal vein are frequently associated with the duodenal inversion.

Incidence. This anomaly is undoubtedly far more common than the number of reported cases would suggest. An incidence of only 0.07 per cent has been reported in 20,000 consecutive upper gastrointestinal

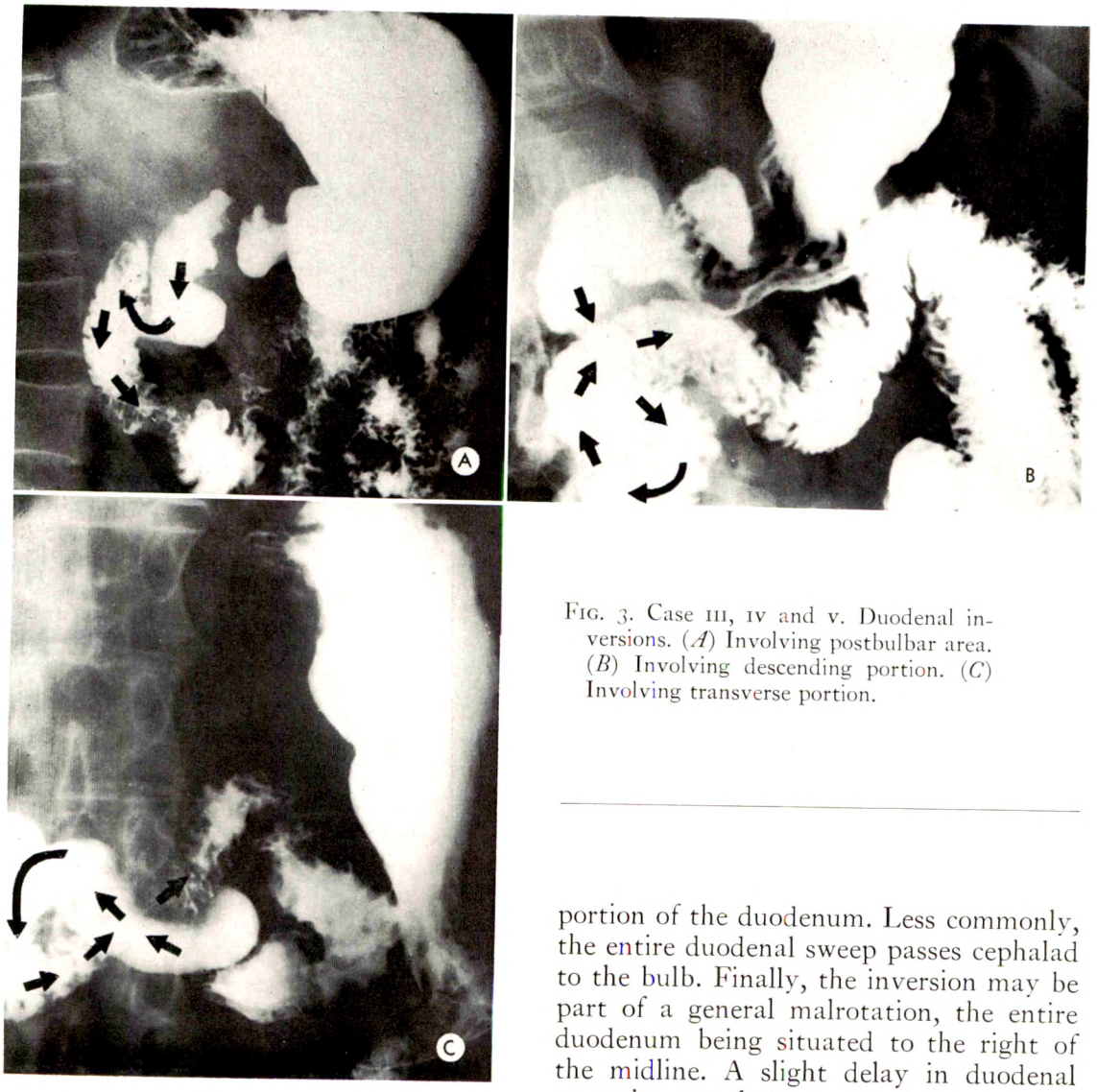


FIG. 3. Case III, IV and V. Duodenal inversions. (*A*) Involving postbulbar area. (*B*) Involving descending portion. (*C*) Involving transverse portion.

examinations.[34] On the other hand, Weinbren and McGregor,[73] alert for this anomaly, discovered 11 cases in one year.

Age and Sex. Duodenal inversions have been seen at all ages of adult life. Males predominate by a ratio of 3 to 1.

Clinical Features. Symptoms rarely occur. In most instances, the inversion is discovered when the patient is being examined for unrelated gastrointestinal ailments.[27]

Roentgen Findings. The most common type is a localized redundancy of the second portion of the duodenum. Less commonly, the entire duodenal sweep passes cephalad to the bulb. Finally, the inversion may be part of a general malrotation, the entire duodenum being situated to the right of the midline. A slight delay in duodenal emptying may be seen, especially when the second portion is markedly redundant.[27]

ILLUSTRATIVE CASES

CASE III, IV and V (Fig. 3, *A*, *B* and *C*). These patients, aged 21, 28, and 63, were examined because of symptoms of peptic ulcer. The duodenal inversions were discovered incidentally.

DUODENAL DIAPHRAGMS

Duodenal diaphragms are web-like projections of the mucous membrane which occlude the lumen of the duodenum to varying degrees. The great majority of reported cases have occurred in the second

portion of the duodenum in close proximity to the ampulla of Vater. They are rarely diagnosed preoperatively. Only a few cases have been described in adults.[44,58,59]

Clinical Features. The history of gastrointestinal difficulty is usually of many years' duration, frequently dating from infancy. Bloating, nausea and vomiting are common. Rarely, the diaphragms cause no symptoms.

Roentgen Findings. The roentgenographic picture is variable. One may see merely dilatation proximal to the lesion. The diaphragm may present as a thin radiolucency extending across the lumen.[58] Despite striking encroachment upon the lumen, only minimal obstruction may occur.[46] On occasion, the diaphragm may balloon-out distally, producing a distinct, barium-filled sac occupying the duodenal lumen. Retained food and fruit pits may cause filling defects within this sac.[59]

CONGENITAL BANDS

Congenital bands which affect the duodenum result from variations in the degree of obliteration of the ventral mesogastrium.[37] They are classified as cholecystoduodenocolic, cholecystoduodenal or duodenoperitoneal, depending upon their major points of attachment.[13,14] The most common anomaly is a band of variable width and thickness, arising from the gallbladder, crossing the second portion of the duodenum and inserting into the hepatic flexure of the colon.

Incidence. The necropsy finding of an abnormal band is extremely common. An incidence as high as 18 per cent has been reported. Only a small number of these exert sufficient influence on the duodenum to be recognized roentgenologically. There is no sex predominance.

Clinical Features. Symptoms are usually absent. In an analysis of 1,200 cholecystectomies, Mahoney[52] found only 18 cases in which symptoms could be attributed to congenital bands. When the band compresses the duodenum, partial obstruction may develop. The patient may complain of postprandial fullness, epigastric pain and vomiting. These symptoms are often of long duration and are usually intermittent.[35,37]



Fig. 4. Case vi. Congenital band. Sharply defined rectangular defect on convex surface of second portion, producing slight obstruction.

Roentgen Findings. Roentgen findings depend on the location of the band and the degree to which it indents the duodenum. There may be a sharply localized defect on the outer margin of the descending duodenum. In other cases, the band causes a sharp angulation of the duodenum. In rare instances, marked dilatation is present proximal to the obstructing band.

ILLUSTRATIVE CASE

Case vi (Fig. 4). J.D., a 38 year old white male, entered the hospital on January 9, 1958 complaining of vomiting and epigastric pain. These attacks occurred 3 to 4 times a month and were of increasing severity.

The physical examination was negative. Except for one 3+ test for occult blood in the stool, the laboratory examination was negative. Four other stool examinations were normal.

An upper gastrointestinal examination revealed a 1.5 cm., sharply defined marginal filling defect on the convex surface of the second part of the duodenum. There was no obstruction at this point.

At laparotomy, a fibro-fatty band, 1 cm. in

width, was seen to cross and indent the duodenum. The band seemed to arise from the posterior abdominal wall. The lesion was transected and the duodenum immediately filled out.

The patient was symptom free 4 months later.

REDUPLICATIONS OF THE DUODENUM

Reduplications of the intestine are cystic structures which contain epithelial, stromal and muscular layers similar to or identical with those of the viscera from which they arise. While the majority are located within the muscular layer of the gut, they may also be submucous, subserous or intramesenteric. Cysts occurring in the duodenum usually drain into the lumen via one or more openings. When the common bile duct empties into the cyst, a communication with the lumen of the duodenum must be present.[11,38] The contents of the cyst depend largely upon what structures empty into it. Thus, the cyst may contain serous fluid, pus, bile and even gallstones.[38] Rarely, the duodenum may be the site of multiple reduplication cysts.[10,62]

Etiologic Factors. The basic embryologic defect is probably associated with failure of complete coalescence of fetal vacuoles. Other theories are that reduplications are the result of epithelial sequestration[40] or that they arise from embryologic diverticula.[49]

Any factor which interferes with drainage will result in enlargement of the cyst. This interference may be the result of stones or inspissated debris, but is more frequently caused by infection of the cyst, with inflammatory edema occluding the routes of drainage. When the cyst becomes large enough to encroach upon the lumen of the duodenum, symptoms of duodenal obstruction may occur.

Incidence. Reduplications of the duodenum are rare. Baroody *et al.*,[4] reviewing the literature in 1956, reported 21 cases in all age groups and added their own case. Our review has yielded 8 adult cases; we add 1 for a total of 9. The incidence of reduplications in the ileum is 10 times as great as in the duodenum.[39,40,61]

Age and Sex. There is no sex predominance. Approximately 40 per cent of all reported cases have been in adults.

Clinical Features. The usual symptoms are those of duodenal obstruction. On occasion, ulceration and bleeding may occur.[67] Submucosal cysts may intussuscept.[11] Jaundice may occur from compression of the biliary tract by the enlarging cyst.

The most common physical finding is a movable, nontender cystic mass in the epigastrium.

Roentgen Findings. Plain roentgenograms may show a well defined epigastric mass of uniform density. The findings on barium study are frequently characteristic. Two roentgen patterns are described. The first is a well defined, oval filling defect. The second, and more characteristic pattern, is a sharply defined, marginal defect in the concavity of the first and second portions of the duodenum. Rarely, the defect may be on the convex surface of the duodenum.[57] It is usually impossible with any certainty to differentiate these reduplications from lipomas, leiomyomas and other intramural tumefactions.

ILLUSTRATIVE CASE

Case VII (Fig. 5, *A* and *B*). E.D., a 48 year old white female, was admitted to The New York Hospital on January 22, 1958 because of abdominal pain of 2 years' duration. This pain was epigastric and occasionally radiated to the back and chest. For 3 months prior to admission she had suffered from vomiting after almost every meal. A gastrointestinal series, performed elsewhere, was said to reveal a pyloric canal ulcer and a "growth" in the duodenum. The patient was put on an ulcer regimen. Four weeks later, the ulcer had healed but the "growth" persisted, and hospitalization was advised.

The physical examination was unremarkable. The laboratory data were normal.

On gastrointestinal study a bilobulated filling defect, approximately the size of a hen's egg, was present in the distal portion of the bulb and post bulbar area. The defect was eccentric and located on the concave side of the duo-

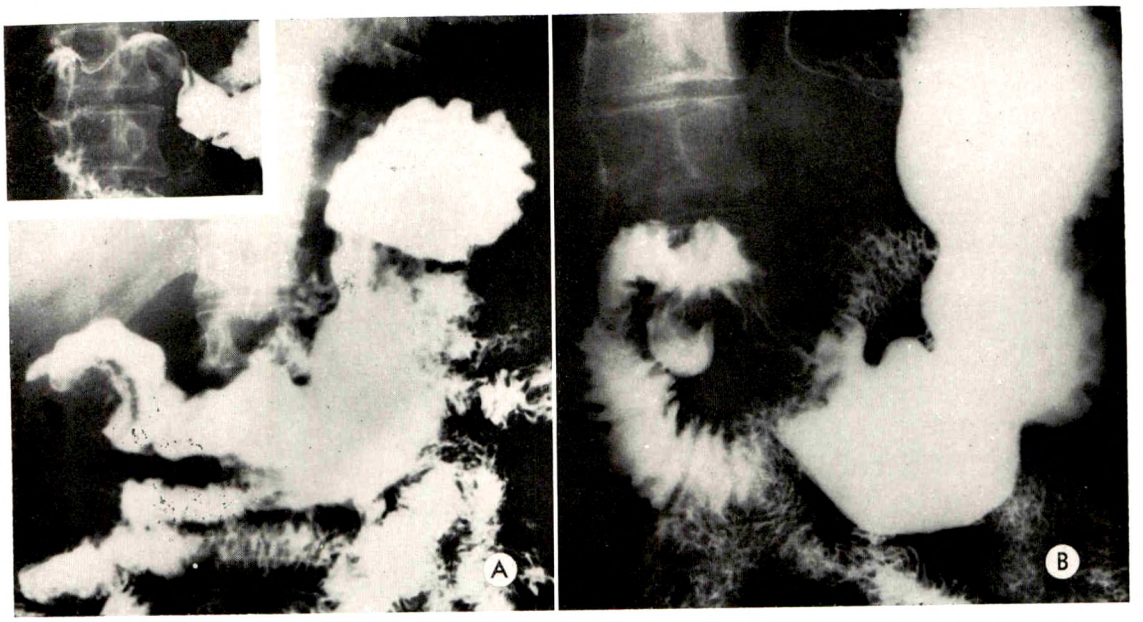


FIG. 5. Case VII. Reduplication cyst. (*A*) Bilobular intramural defect on concave surface of first and second portions. (*B*) Internal drainage has converted cyst into "diverticulum."

denum. It was felt that this represented an intramural neoplasm of the duodenum.

At operation, a cystic lesion, measuring 8 by 2 cm., was found in the wall of the duodenum. The cyst contained 30 ml. of cloudy fluid. When tested, this fluid revealed 602 units of amylase. The cyst was opened internally, creating a common channel with the duodenal lumen. The patient made an excellent recovery. Gastrointestinal series performed 4 months following discharge showed a large diverticulum-like out-pouching in the area previously occupied by the cyst.

Microscopic examination of the cyst wall showed duodenal mucosa and several nests of ectopic pancreas. The pathologic diagnosis was reduplication of the duodenum.

ANNULAR PANCREAS

Annular pancreas is the occurrence of a ring of pancreatic tissue which encircles the duodenum, almost invariably, in its second portion. In some instances, the ventral part of the annulus has become a thick, fibrous band.

Etiologic Factors. When symptoms arising from an annular pancreas are delayed until adult life, some complicating condition must be suspected. Pancreatitis has been found in about one-fifth of operated cases.[51,75] It has been reasoned that the edema of the inflamed pancreas results in sufficient narrowing of the annulus to cause duodenal obstruction.[48] In approximately 30 per cent of cases, a duodenal ulcer is found. It is not known whether the ulcer precedes the duodenal obstruction or is a consequence of it. It is known that obstruction of the duodenum proximal to the ampulla of Vater frequently causes duodenal ulceration, presumably as a result of decreased alkaline backflow into the bulb. In some instances, the dilated and redundant duodenum proximal to the annular pancreas suddenly kinks, converting a subclinical obstruction into a clinically significant one.[71,75]

Incidence. Prior to 1950, annular pancreas was regarded as a curiosity diagnosed only at the time of surgery or necropsy. In the past decade, the preoperative diagnosis has been made with far greater frequency.[7,22] Lundquist[51] has accounted for 111 cases in adults, thus dispelling the notion that this is a disease of infancy only.

Age and Sex. Friedman,[30] in an analysis of 86 proven cases, found 45 in infants up to

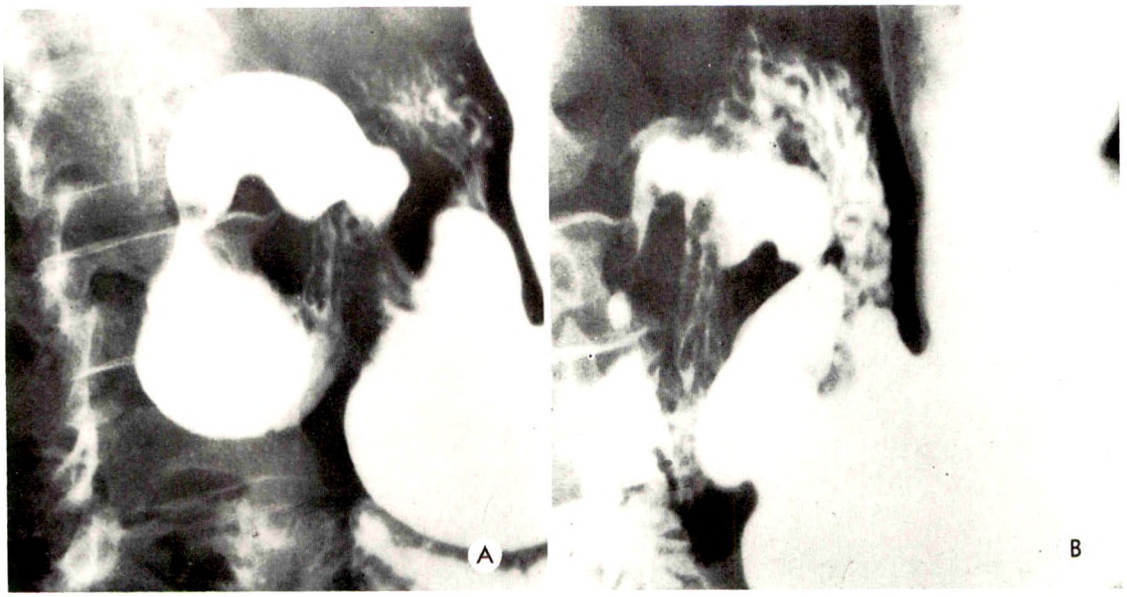


Fig. 6. Case VIII. Annular pancreas. (*A*) Hour-glass narrowing of second portion of the duodenum. Impacted food particle. (*B*) Ulcer niche in narrowed segment.

3 months of age and 41 in adults 17 to 74 years of age. Males predominate by a ratio of 2 to 1.[51]

Clinical Features. Symptoms related directly to the annular pancreas are those of duodenal obstruction. Postprandial fullness, epigastric pain, eructation and vomiting are common. Equally common are symptoms related to concomitant disorders such as duodenal ulcer and pancreatitis.[5] Less common symptoms are hemorrhage,[51] jaundice[75] and hypoglycemic episodes. It should be emphasized that many patients with annular pancreas are entirely without symptoms.

Roentgen Findings. The roentgen findings largely depend upon the degree of obstruction present. With complete obstruction the duodenum is dilated and redundant proximal to the lesion. With lesser degrees of obstruction, one may see an hour-glass shaped annular narrowing just proximal to the ampulla of Vater. The narrowed area may be angulated medially. The mucosa is intact but may be atrophic.[63] In unobstructed cases, the only finding may be a notch-like defect, 1 to 3 cm. in length, on the convex border of the descending duodenum. In this latter type, a roentgenologic diagnosis of annular pancreas can frequently be suggested.[5,22,48]

We have seen one patient with an ulcer at the point of maximum constriction. To our knowledge, ulceration of this type has been previously described only once.

The differential diagnosis includes postbulbar ulcer, regional enteritis, tumors of the duodenum and pancreas, and other congenital anomalies.

ILLUSTRATIVE CASES

Case VIII (Fig. 6, *A* and *B*). C.C., a 66 year old white female, was admitted to The New York Hospital on March 15, 1960 because of vomiting and epigastric pain of 5 years' duration. In the 6 months prior to admission she had lost 20 pounds.

At physical examination it was noted that the patient belched frequently. There was slight right upper quadrant tenderness. The physical examination was otherwise negative. Laboratory examination was normal.

An upper gastrointestinal examination revealed an hour-glass type of narrowing in the descending duodenum. At the most constricted portion, there was a persistent barium collection resembling an ulcer niche. At 4 hours, 40

per cent of the barium meal was retained in the stomach.

At operation there was an annular pancreas surrounding and constricting the duodenum. There was an associated ulcer and some cicatrization. A pyloroplasty and posterior gastroenterostomy were performed. The strictured duodenum was dilated. Postoperatively, the patient did well.

Case ix (Fig. 7). J.L., a 68 year old white male, was re-admitted to The New York Hospital on September 4, 1951 because of right upper quadrant and right shoulder pain. He had been hospitalized 3 months previously, at which time a diagnosis of liver abscess had been made. A gastrointestinal series at that time had shown an area of narrowing in the duodenum, just at the level of the ampulla of Vater. The mucosa was intact in this area. A moderate delay in passage of the barium meal was noted. The impression was that of extrinsic pressure.

At the time of re-admission, it became apparent that the liver abscess had recurred. The patient was explored and the abscess drained. The duodenum also was explored. There was a band of pancreatic tissue, 2 cm. in width and 3 mm. thick, surrounding the duodenum. The lumen of the duodenum appeared compromised. The surgeon was able to resect this ring of pancreas, but found that there was no underlying muscle wall in the duodenum. Sutures were placed in the duodenum in such a fashion as to strengthen the wall at this point.

The patient was seen 7 years later and had no gastrointestinal complaints.

ABERRANT PANCREAS

Aberrant pancreas, also known as ectopic, accessory or heterotopic pancreas, is the occurrence of a nidus of pancreatic tissue in a location entirely separate from the pancreas itself. These foci vary in size from 1 mm. to over 4 cm. in diameter. They may be found anywhere in the gastrointestinal tract, but are most commonly observed in the stomach, duodenum and jejunum.[28]

The aberrant pancreas may be composed of acini, ducts and islands of Langerhans, or may be deficient in one or two of these elements. The lesion may be submucosal, intramuscular, subserosal or intramesenteric. The submucosal location is the most common.[2,6,28]

Incidence. The postmortem discovery of an aberrant pancreas in the duodenum is a very common occurrence. In a meticulous study by Feldman and Weinberg,[28] an incidence of 12.5 per cent was reported. In more than one-half of these cases, the anomalous focus measured less than 5 mm. in diameter.

The duodenum and stomach are the most commonly involved viscera, each accounting for more than one-fourth of the cases. The jejunum is involved in 15 per cent of cases.[2] The gastric lesions tend to produce more symptoms, and are more easily detected roentgenologically. Thus, lesions of the stomach are diagnosed more frequently in life than those in the intestines.[2,24,26,53,65]

Age and Sex. All symptomatic cases have occurred in adults. There seems to be a

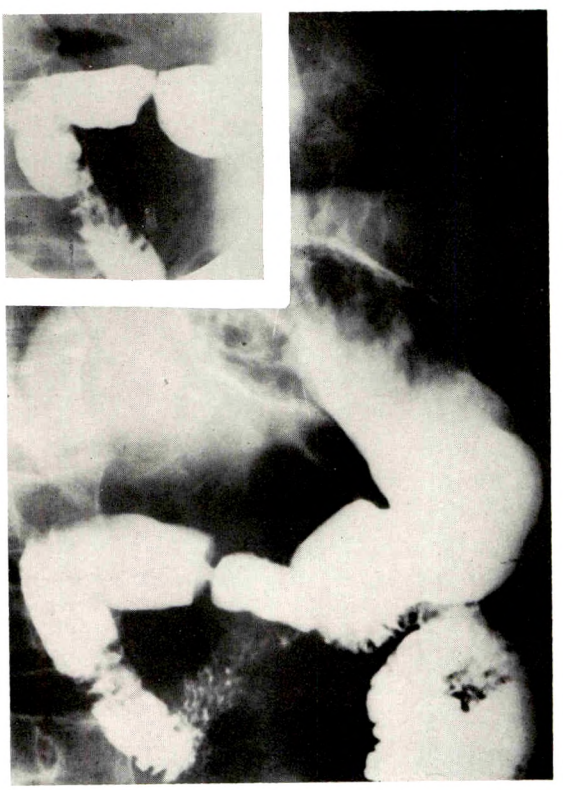


Fig. 7. Case ix. Annular pancreas. Faint ring-like defect at ampulla of Vater. Mucosa intact.



FIG. 8. Case x. Aberrant pancreas. Smooth intramural defect in bulb. Central duct not visualized.

slight male predominance.[2,53]

Clinical Features. Most patients with aberrant pancreas in the duodenum are asymptomatic. When symptoms occur, they usually simulate peptic ulcer disease. In a few cases, actual ulceration is found in the aberrant pancreas or in the adjacent mucosa.[15,41,50] In many instances, removal of the ectopic focus does not alleviate the patient's symptoms. Eklöf[24] has concluded that these ulcer-like complaints exist independently of the aberrant pancreas.

Foci of aberrant pancreas are subject to all the ills of the pancreas itself. Pancreatitis, fat necrosis, cyst formation and neoplastic degeneration have been reported.[8,23] Other complications are intussusception,[9] hemorrhage,[56] and obstruction.[12] There have been recent reports of hyperinsulinism occurring as the result of islet cell tumors in heterotopic pancreas.[36,38]

Roentgen Findings. The discovery of a round or oval, smooth, well-demarcated filling defect in the duodenum suggests the presence of a benign tumor. In many cases, one cannot differentiate between aberrant pancreas and such tumefactions as Brunner's glands, fibromas, lipomas, adenomas and leiomyomas. However, in about 50 per cent of cases of ectopic pancreas, a small fleck of barium is observed in the center of the filling defect. This corresponds to the ostium of a ductal structure, and, when seen, is almost diagnostic of ectopic pancreas.[24,42,43,53] Ulceration of a polyp or leiomyoma may resemble this, but the fleck is more likely to be eccentrically placed. On occasion, a duodenal ulcer with a surrounding "halo" of edema may simulate ectopic pancreas.

In rare instances, patients with aberrant pancreas may exhibit duodenal stenosis, ulceration and intussusception.[9]

ILLUSTRATIVE CASE

CASE X (Fig. 8). L. de P., a 55 year old white female, entered The New York Hospital on January 23, 1954 because of abdominal pain. For 4 years the patient had suffered from attacks of upper abdominal crampy pain, relieved by belching. These episodes occurred sporadically until 4 months prior to admission when they began to occur one or two times a day. She had lost 12 pounds. She had vomited only twice in 4 years. A gastrointestinal series performed in the out-patient department revealed a filling defect in the duodenal bulb. She was admitted for investigation. Past history revealed diabetes mellitus diagnosed 3 years prior to admission.

Physical examination was negative except for obesity. Laboratory examination showed changes secondary to diabetes. Stool guaiac tests were 1+, 3+, 2+, and trace in 4 examinations. Gastric cytology was Papanicolaou positive, Class II.

Gastrointestinal examination revealed a 2.5 cm. filling defect in the bulb identical to that seen on the previous examination.

An exploratory operation was performed. The pylorus was opened and the antrum and bulb palpated. No mass was found. There was an area of induration in the duodenal wall just distal to the pylorus. This was biopsied. The patient became hypotensive on the first postoperative day and despite administration of blood and vasoconstrictors she expired on the second postoperative day.

Microscopic examination of the biopsy specimen revealed aberrant pancreatic acini and

We are indebted to Drs. E. Ten Eyck and D. Law for advice and assistance concerning Case XII. This case is the subject of an article by these authors, presently in print.

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REGIONAL ENTERITIS OF THE DUODENUM*

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REGIONAL enteritis is not a common disease, and involvement of the duodenum is rare. In the series of 600 cases of regional enteritis reported from the Mayo Clinic,[10] the duodenum was involved in only 3 patients. Recently, a patient with signs and symptoms referable to the upper gastrointestinal tract was shown to have regional enteritis of the duodenum and proximal jejunum. This unusual manifestation of regional enteritis prompted a brief review of the literature and a case report.

Crohn, Ginzberg and Oppenheimer[4] reported 14 cases of a new clinical and pathologic entity, a nonspecific, granulomatous inflammation involving the terminal portion of the ileum, in 1932. Because of the rather specific location of the disease in their patients, they proposed the name of "terminal ileitis." Soon, however, the same pathologic process was described in the proximal ileum, the jejunum, the duodenum and even in the stomach.[2,3,5,9] Because of the diffuse nature of this disease, it is now referred to as regional enteritis, although some[7] still prefer the term "chronic nonspecific granulomatous inflammation" suggested by Comfort *et al.*[3] in 1950.

Specific duodenal involvement has been rare. McGarity[6] in 1957 could find only 25 cases of duodenal regional enteritis. He summarized these cases and added a case of his own. There are at least 7 other cases reported[1,7,8] that are not included in his review.

Many of the cases reported as showing duodenal regional enteritis developed this finding in the terminal stage of their disease with involvement of the entire small intestine. In others unexpected duodenal involvement was found at postmortem examination.

A few of the reported cases, however, presented a strikingly different clinical picture of symptoms solely referable to the upper gastrointestinal tract. The second and third cases reported by Richman *et al.*[7] and the first case reported by Berk[1] are typical examples of the clinical and roentgenologic findings of regional enteritis involving the duodenum early in the disease. The present case is reported to add another example of this unusual manifestation of regional enteritis to the literature and to re-emphasize the clinical and roentgenologic findings.

REPORT OF A CASE

C. F., a thirty-seven year old white male, was in good health until 1956, when he was found to be anemic. At that time, he had vague upper abdominal discomfort, and the diagnosis of duodenal ulcer was made on the basis of rather equivocal roentgen findings of a slightly thickened, irregular mucosal pattern in the duodenal bulb. He was well for several years and then had a recurrence of his upper abdominal discomfort in 1958. He was somewhat improved by a bland diet and antispasmodics.

In 1959, he developed progressive weight loss, nausea and vomiting and was admitted to the U. S. Naval Hospital, Oakland, California. At that time, upper gastrointestinal studies revealed mucosal irregularity of the second portion of the duodenum with partial obstruction (Fig. 1). He was explored and found to have regional enteritis of the duodenal loop. A small segment of the distal ileum was also involved. A resection was not performed at that time, and he responded well to a short course of radiation therapy to the abdomen.

He was asymptomatic for fourteen months, and then in the spring of 1960, he again developed nausea, vomiting, weight loss, cramping abdominal pain, and intermittent, low-grade fever. In the two months prior to his admission,

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he lost a total of 25 pounds. He was admitted to the U. S. Naval Hospital, San Diego, California, in June of 1960. On admission, physical examination revealed an emaciated, dehydrated white male with a low-grade fever. The only important physical finding was tenderness to palpation in the mid-epigastrium. All laboratory studies were within normal limits. An upper gastrointestinal study (Fig. 2) revealed a dilated, atonic stomach with some fluid retention. The duodenal bulb was large and flaccid with complete loss of mucosal pattern. The second portion of the duodenum was narrow and irregular and did not fill out to a normal contour. The distal duodenum was also dilated and irregular with a segment of narrowing involving the third and fourth portions of the duodenum to the region of the ligament of Treitz. The proximal 10 to 15 cm. of jejunum was also narrow and irregular. The remainder of the small bowel as visualized on serial roentgenograms was thought to be within normal limits. A barium enema study revealed slight mucosal thickening and irregularity of the terminal 4 cm. of ileum consistent with regional enteritis (Fig. 3).

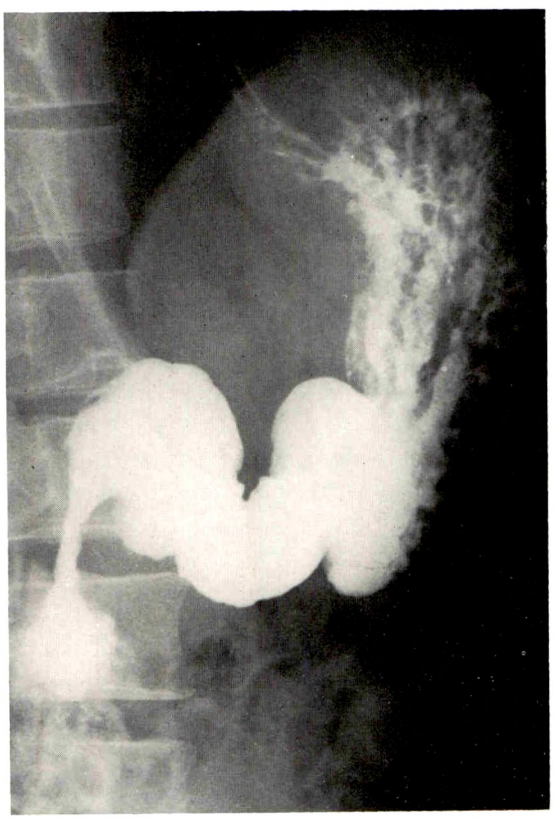


Fig. 1. Upper gastrointestinal study, in 1959, revealing mucosal irregularity of the duodenal loop with partial obstruction of the second portion of the duodenum.

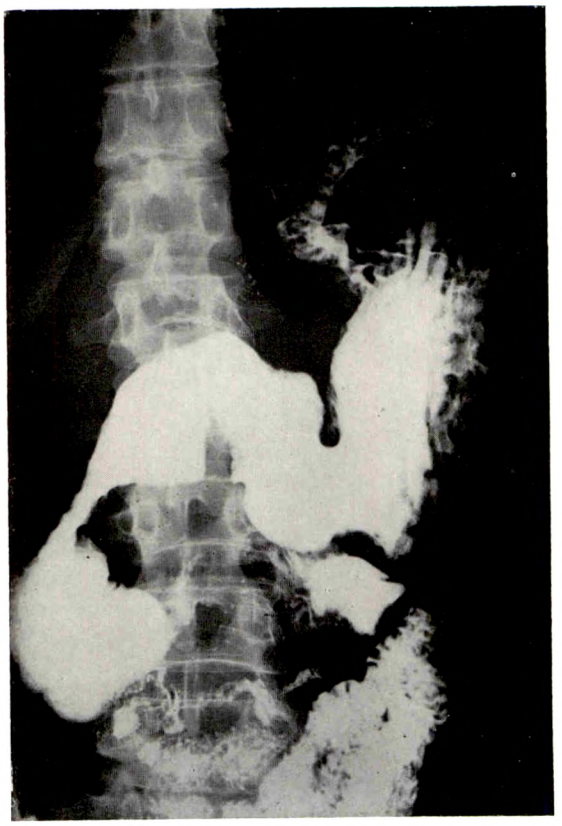


Fig. 2. Upper gastrointestinal study, June 1960, revealing increased obstruction of the second portion of the duodenum with mucosal irregularity of the distal duodenal loop and the proximal jejunum.

Two weeks after admission, the patient was explored and found to have extensive thickening and narrowing of the duodenal loop, the first 15 cm. of jejunum and the terminal 4 cm. of ileum. A bilateral vagotomy and a posterior gastroenterostomy were performed, with resection of the involved segments of jejunum and terminal ileum. The patient improved rapidly postoperatively with absence of fever, improved appetite, and a 10 pound weight gain during the first month. The pathologic report of the resected segments revealed changes typical of regional enteritis.

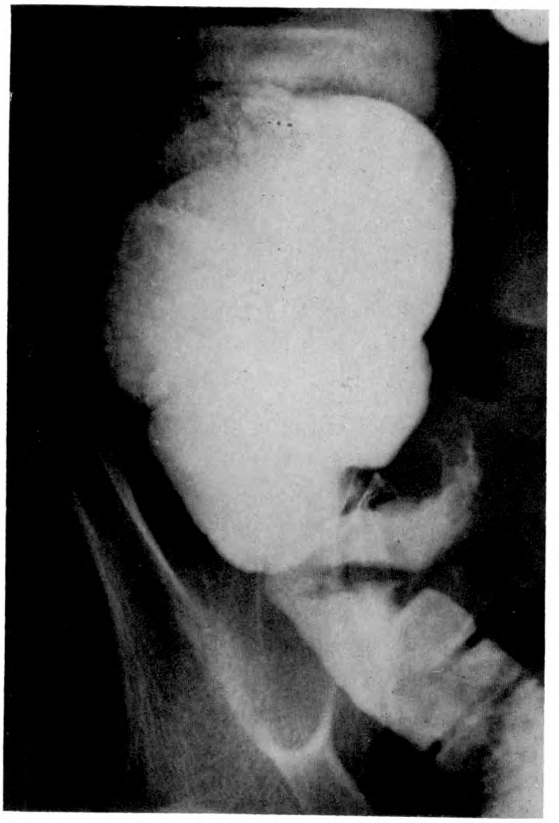


FIG. 3. Barium enema study, June 1960, revealing minimal mucosal thickening in the distal loop of ileum.

DISCUSSION

The gross and microscopic pathologic picture of regional enteritis involving the duodenum is similar to that of the distal small bowel. This has been well reviewed[10] and will not be included in this report. The clinical and roentgenologic findings in duodenal regional enteritis are strikingly different from the symptoms and roentgen manifestations usually associated with this disease.

Clinically, upper gastrointestinal signs and symptoms of nausea, vomiting, cramping upper abdominal pain and gastric retention dominate the picture. As in the present case, there may be dehydration and emaciation. The usual symptoms of right lower quadrant abdominal pain and diarrhea are not prominent.

Roentgenologically, mucosal alterations and loss of normal intestinal motility are the first findings. Later in the disease, narrowing of the intestinal lumen due to edema and inflammatory changes, and finally fibrosis produce gastric retention and duodenal obstruction. In some cases, the typical "string sign" of partial obstruction with narrowing of the intestinal lumen may be demonstrated. Skip areas of involvement with segments of normal or dilated bowel between may be demonstrated by small bowel study. A diseased terminal ileum is best shown by barium enema examination.

CONCLUSION

It is felt that regional enteritis should be included in the differential diagnosis of obstructing lesions of the duodenum, even if pre-existing regional enteritis of the distal small bowel is not known. If the typical "string sign" is demonstrated with skip areas of involvement or if distal ileal involvement is noted, the diagnosis is established with certainty.

SUMMARY

A case of regional enteritis of the duodenal loop and proximal jejunum is presented with a brief review of the clinical findings and roentgenologic picture.

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GRANULOMATOUS COLITIS (CROHN'S DISEASE OF THE COLON)*

ROENTGEN FEATURES

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IT IS becoming generally accepted that there is a type of chronic colitis which has pathologic features similar to those seen in granulomatous disease of the small bowel, *i.e.*, Crohn's disease[2,3,7,11,13] In the British literature[3,7] this condition has been called "primary Crohn's disease of the colon." It may also be referred to as "granulomatous colitis."[2,4] Since the original report of regional or granulomatous ileitis by Crohn, Ginzburg and Oppenheimer[5] there have been numerous case reports of the same disease in other parts of the gastrointestinal tract proximal to the ileum, most commonly in the jejunum, but also in the duodenum, the stomach and esophagus. Recognition of this disease process in these areas is facilitated by the fact that other nonspecific chronic inflammatory diseases which resemble Crohn's disease are not common in these organs. In contrast, however, the recognition of granulomatous disease of the colon has been delayed by the much greater frequency of chronic ulcerative colitis in this organ and the fact that granulomata, presumably of the foreign body type, may be present in ulcerative colitis. Moreover, in the late stages of granulomatous colitis with diffuse ulceration, it may be difficult to detect the characteristic noncaseating tubercles of granulomatous disease.[3] Numerous sections, particularly of nonulcerated areas, may be necessary before epitheloid nodules are discovered. Nevertheless, over a period of years, there have been several reports[1,6,10,14] of chronic colitis distinct from ulcerative colitis. A variety of names has been used for this condition. Many of these designations were based on the fact that the reported cases demonstrated only limited involvement of the colon and, specifically, appeared to spare the sigmoid and rectum. As a result, terms such as "segmental" and "regional"[1,6,10,11] were applied to this condition. In retrospect, it appears that the early emphasis on the segmental nature of this condition was based on less advanced stages of the disease since such cases were more readily recognized and differentiated from chronic ulcerative colitis. It is true that limited involvement and sparing of the rectum and sigmoid are more common in granulomatous than in ulcerative colitis. Nevertheless, it is now clear that granulomatous colitis may involve the entire colon and that it also may be confined to the rectum and sigmoid. Moreover, when the term "regional" is used, it is difficult to tell whether the author is inferring that the disease is similar to Crohn's disease or that it is simply limited in extent or location. It therefore seems advisable to discard the terms "regional" or "segmental" in naming this variety of chronic colitis.

In the large majority of cases of granulomatous disease of the small bowel, *i.e.*, classic Crohn's disease, the disease process remains confined to the small bowel. There are, however, several exceptions to this. In one group of patients, there is direct extension through the wall of the small bowel into an adjacent portion of the colon, usually the cecum or sigmoid (Fig. 1). As a result of such spread and fistula formation, the granulomatous process in the colon may become chronic and spread along the long axis of this viscus. This form of granulomatous disease of the colon may be aptly termed secondary. In a second group of

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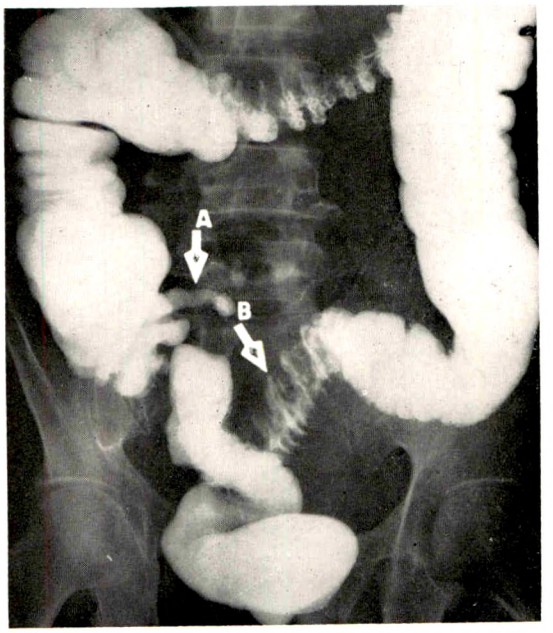


Fig. 1. Granulomatous ileitis with involvement of an adjacent loop of sigmoid. Barium enema study shows a segment of limited distensibility in the mid-sigmoid (arrow B) with coarse thick folds on its superior and medial aspect. The remainder of the colon is normal. A short segment of the terminal ileum (arrow A) is narrowed with effaced mucosal pattern.

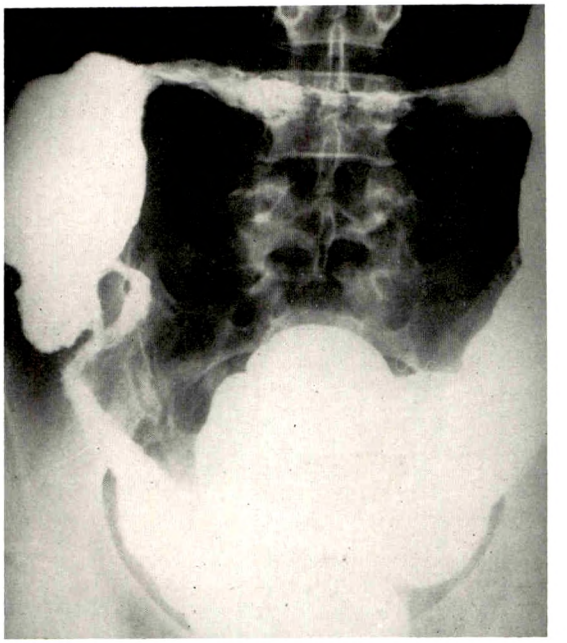


Fig. 2. Granulomatous ileitis with a skip area in the transverse colon. The terminal ileum is narrowed with marked irregularity of its mucosal surface. The caput coli is slightly irregular in contour. The transverse colon is also narrowed and shortened with no normal mucosal pattern. The ascending colon intervening between the narrowed terminal ileum and transverse colon is increased in caliber.

patients, in addition to granulomatous disease of the small bowel, there is also involvement of the colon when the patient is first seen. This group with synchronous or concurrent involvement of small bowel and colon may be further subdivided into two subvarieties. In one, the disease process in the colon resembles a skip area in the sense that the segment involved is remote from the diseased ileum (Fig. 2). In another, the disease process in the colon is continuous with similar disease in the terminal ileum (Fig. 3). A third group of patients would include those who, after operative intervention for granulomatous disease of the ileum, develop a segmental granulomatous lesion in the colon usually adjacent to the anastomosis. In all of these groups, it is reasonable to assume that the disease process in the colon has the same etiology as the disease in the small bowel. At the present time, however, despite similarity in histologic findings, it would not be warranted to assume that granulomatous disease confined to the colon is identical to classic Crohn's disease of the small bowel. While this appears likely, there must be some reservation until the etiologic agent is clarified.

PATHOLOGY

The pathology of the granulomatous disease process in the colon has been well described.[3,7,11,12] Often, the gross appearance of the bowel, specifically the marked thickening of the bowel wall, is as useful diagnostically as the demonstration microscopically of noncaseating granuloma or tubercle formation. All layers of the bowel wall are thickened and there is often excess fat adherent to the serosa. In granulomatous disease of the colon, the presence of long longitudinal ulcerations often extend-

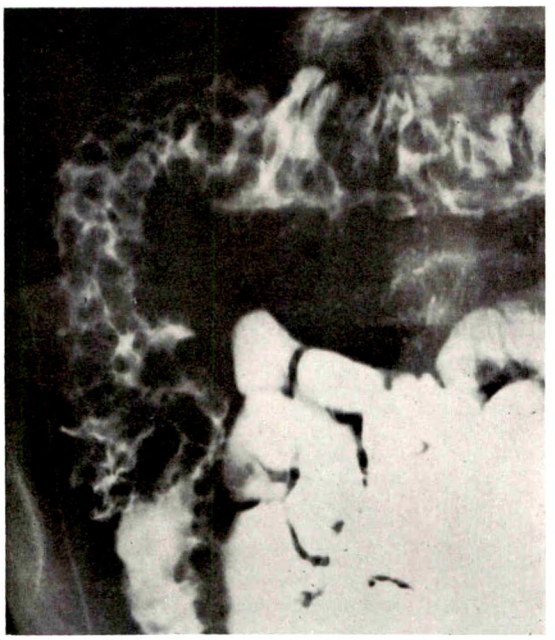


Fig. 3. Granulomatous ileitis and colitis in direct continuity. The terminal ileum and cecum and ascending colon show marked pseudopolypoid projections. These are demarcated by several serpiginous elongated ulcerations with numerous transverse connections. The ileocecal valve is effaced. This type of case with disease in continuity appears to be common in younger individuals. (Reproduced with permission from *Radiology*.)

ing for many inches is quite characteristic. The longitudinal ulcerations show communicating lateral branches which appear grossly as thin, deep fissures. These fissures apparently represent the early stages of the process which leads to fistulization. Skip areas of disease in the course of the colon are another hallmark of the granulomatous process. In other words, multiple diseased segments separated by normal bowel are an expected and common feature of granulomatous colitis and are rare in ulcerative colitis. A skip area may be quite short but nevertheless obvious because it is distinctly narrowed. In other instances, a skip area may be represented only by localized submucosal thickening on one wall with or without overlying ulceration. While mucosal ulceration is ordinarily present when patients have symptoms, the lesions begin in the wall of the bowel and ulceration is a secondary feature. With ulceration, the intervening mucosa and submucosa are congested and inflamed. The combination of ulceration and intervening swollen areas results in a coarse, irregular, "cobblestone" pattern. These islands of residual inflamed mucosa may be rather discrete and have been described as pseudopolypoid. However, the formation of inflammatory polypi with an elongated pedicle is rare in granulomatous disease. Shortening of the colon may be a prominent feature in the late stages. Extensive regrowth of atrophic epithelium—as seen in inactive ulcerative colitis—is not a feature of granulomatous disease. Microscopically, the presence of noncaseating tubercle-like nodules containing epitheloid cells and small Langhans type multinucleated giant cells is the chief diagnostic feature. A diffuse chronic inflammatory granulomatous process involving all layers of the bowel wall showing numerous histiocytes, plasma and lymphoid cells as well as fibrotic changes is typical.

CLINICAL FEATURES

The clinical features of granulomatous colitis of the primary type have not been sufficiently well defined to permit clear differentiation from ulcerative colitis. In general, however, the impression at present is that, in granulomatous disease, the patients have a more chronic and unremitting course, that stricture and fistula formation are more common, that acute phases resembling fulminating ulcerative colitis with dilatation of the colon are not seen, and that there is no increased incidence of colonic carcinoma. We have been impressed by the fact that the disease process may be seen in young individuals in the first and second decades, as well as in patients in the fifth and sixth decades. From a therapeutic point of view, the current impression is that segmental resection or bypass operations for limited granulomatous disease are more likely to be curative than in ulcerative colitis. However,

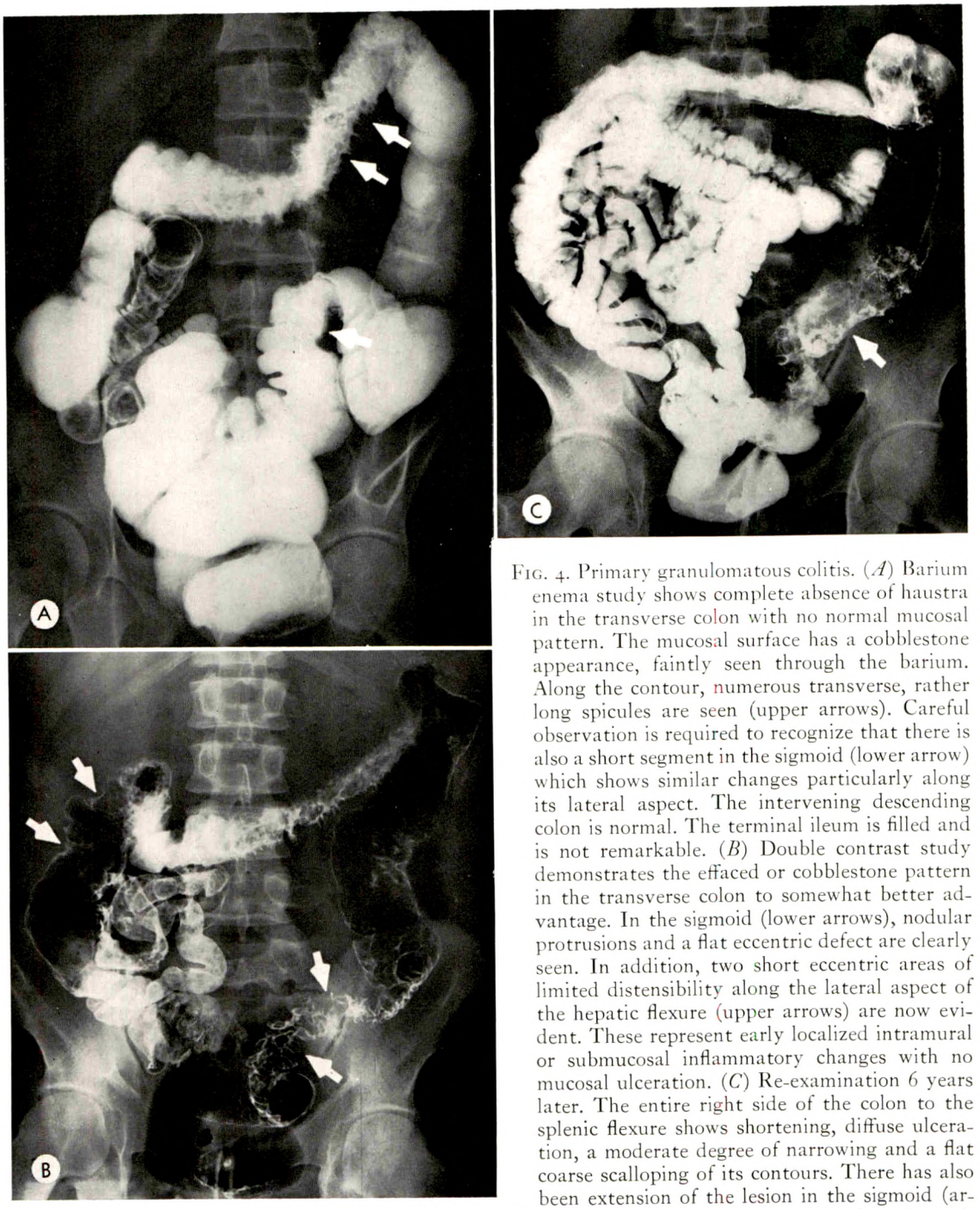


Fig. 4. Primary granulomatous colitis. (*A*) Barium enema study shows complete absence of haustra in the transverse colon with no normal mucosal pattern. The mucosal surface has a cobblestone appearance, faintly seen through the barium. Along the contour, numerous transverse, rather long spicules are seen (upper arrows). Careful observation is required to recognize that there is also a short segment in the sigmoid (lower arrow) which shows similar changes particularly along its lateral aspect. The intervening descending colon is normal. The terminal ileum is filled and is not remarkable. (*B*) Double contrast study demonstrates the effaced or cobblestone pattern in the transverse colon to somewhat better advantage. In the sigmoid (lower arrows), nodular protrusions and a flat eccentric defect are clearly seen. In addition, two short eccentric areas of limited distensibility along the lateral aspect of the hepatic flexure (upper arrows) are now evident. These represent early localized intramural or submucosal inflammatory changes with no mucosal ulceration. (*C*) Re-examination 6 years later. The entire right side of the colon to the splenic flexure shows shortening, diffuse ulceration, a moderate degree of narrowing and a flat coarse scalloping of its contours. There has also been extension of the lesion in the sigmoid (arrow) with diffuse ulceration. This patient also suffered from perianal fistulae and abscesses but sigmoidoscopy was negative.

recurrence in both conditions in the residual colon is not infrequent. It is of interest that, in the series of primary Crohn's disease of the colon reported by Cornes and Stecher[3] no recurrence in the small bowel was seen after surgical treatment in a limited follow-up group. From previous experience with the high recurrence rate in granulomatous

disease of the small bowel, this is a surprising result. Brooke[2] has reported small bowel recurrence in several patients with granulomatous colitis after total proctocolectomy.

ROENTGEN FEATURES

From the roentgen point of view, the suspicion that an inflammatory process in the colon is granulomatous in character is immediately raised when there is coincident granulomatous disease of the small bowel. It is therefore important to perform a small bowel series whenever inflammatory disease of the colon is found. In the past, a significant number of patients were said to have both granulomatous disease of the small bowel and chronic ulcerative colitis. It would appear that with the recognition of granulomatous colitis as a disease sui generis, the number of patients said to have both diseases has substantially diminished. It is, however, probably incorrect to say that this combination never occurs,[12] neither is it possible to assume that, because granulomatous disease is present in the small bowel, the process in the colon is also granulomatous. Because of this, and because granulomatous disease may be primary or confined to the colon, it is essential that roentgen features characteristic of granulomatous disease be identified before the diagnosis is made.

As pointed out above, in the late stages of granulomatous colitis with diffuse ulceration (Fig. 4, *A*, *B* and *C*), differentiation from ulcerative colitis may be difficult or impossible pathologically. This is also true roentgenologically. In less advanced cases, however, the features that are characteristic of the gross specimen may also be recognized on roentgen examination. In this context, roentgen examination ordinarily refers to barium enema examination. It must be emphasized, nevertheless, that useful and often important information can be gained from late roentgenograms after administration of barium by mouth, *e.g.*, as part of the "small bowel series." The partial or progressive filling of the colon achieved in this way may reveal characteristic changes difficult to demonstrate in any other fashion. Areas of "spasm" or irregularity in distention may be more evident than on barium enema examination.



Fig. 5. Granulomatous colitis. The left side of the colon down to the rectum is markedly shortened and narrowed with an absent mucosal pattern. This segment of the colon acted simply as a conduit with little change in caliber during filling and emptying. The right side of the colon is distended with a large amount of fecal material. Despite the absence of characteristic changes, the rigidity of the wall of the involved segment is highly suggestive of granulomatous disease.

The chief roentgen diagnostic features of granulomatous colitis include: (1) skip areas; (2) longitudinal ulcerations; (3) transverse fissures; (4) eccentric involvement and pseudodiverticula; (5) narrowing with relatively rigid walls indicating intramural fibrotic changes; (6) marked pseudopolypoid changes producing a coarse cobblestone pattern; and (7) internal fistulae. These findings are essentially the same as those described for granulomatous disease of the small bowel.[8,9] The involved area is usually limited in extent (Fig. 5) or more than one such area is present with interven-

ing segments free of disease (Fig. 6). Occasionally, an intervening segment may become markedly dilated (Fig. 7) presumably as a result of stasis due to narrowing of the lumen above and below—a partial closed-loop type of obstruction. Skip areas must be searched for carefully (Fig. 4, *A*, *B* and *C*) since eccentric involvement of one wall may present as a small flat or nodular filling defect easily obscured by complete filling and distention. Eccentric involvement due to ulceration on one wall may present simply as a somewhat hazy straightening of one contour. In such instances, localized irritability or spasm may draw attention to the involved segment which may be only 1–2 cm. in length. In other cases, the presence of eccentric ulceration is suspected because the opposite wall shows pseudodiverticula. This is due to the fact that the ulceration along one wall limits elongation of the bowel, and, as a result, the opposite uninvolved wall becomes folded or plicated durnig filling (Fig. 8). The long longitudinal ulcerations represent progression of this type of ulceration. Such longitudinal ulcerations (Fig. 9) are frequently multiple—two or three, perhaps related to the normal tenia and the mesenteric attachment of the colon. A long ulceration of this type along one wall may simulate an intramural sinus tract (Fig. 10) as seen in diverticulitis. When multiple transverse linear ulcers join the longitudinal ulcers, a cobblestone pattern (Fig. 6) is seen within which discrete longitudinal ulceration may be difficult to discern. In late stages, no mucosal pattern will be evident because of diffuse ulceration (Fig.



Fig. 6. Granulomatous colitis. The distal half of the transverse colon shows limited distensibility with gross pseudopolypoid mucosal changes forming a coarse cobblestone pattern. There is in addition a short narrowed area at the junction of the descending colon and the sigmoid. The narrowing is eccentric and the mucosal pattern over this short segment appears hazy and irregular. In the absence of segmental disease elsewhere, differentiation of the sigmoid lesion from carcinoma would be quite difficult.



Fig. 7. Granulomatous colitis. The descending colon and the rectum (arrows A and C) are obviously shortened. The rectum is narrowed. The descending colon shows diffuse superficial ulceration with thick, tortuous, longitudinal folds and small polypoid projections. The sigmoid (arrow B) intervening between the descending colon and the rectum is unusually distended in a saccular fashion. The fuzzy contour of this sac is the result of retained material and superficial inflammatory changes resulting from stasis.



Fig. 8. Granulomatous colitis. The entire left side of the colon including the rectum is involved. Long longitudinal ulcers are indicated by the double densities along the margins of the descending colon. The mid-transverse colon shows pseudodiverticula along its inferior aspect opposite the shortened ulcerated superior margin. Numerous transverse fissure ulcers extending out from the lumen are present throughout the descending colon and sigmoid. In places, these end in small abscess cavities in the wall of the bowel. (Reproduced with permission from *Radiology*.)

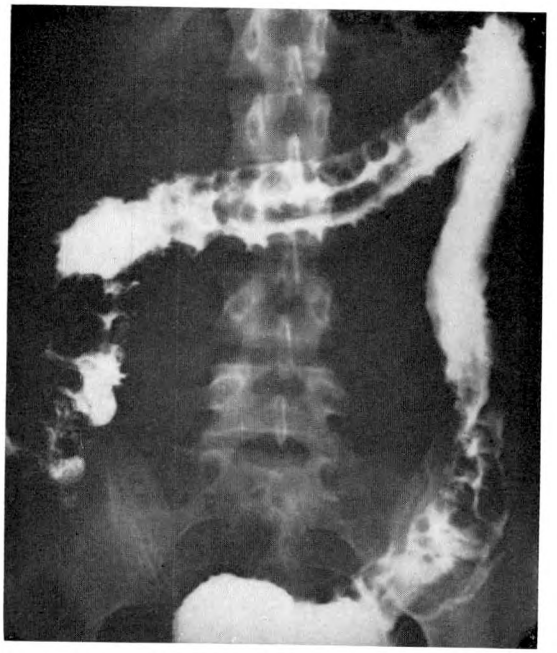


Fig. 9. Evacuation film of barium enema examination. When completely filled with barium, the marked mucosal changes seen on this roentgenogram were not evident. Emptying of the barium was incomplete. Practically the entire colon shows marked mucosal changes. In the transverse colon, however, the long longitudinal ulcers are clearly evident with lateral communicating channels producing a coarse cobblestone pattern.



Fig. 10. Granulomatous colitis. A long eccentric longitudinal ulcer (arrows) is present along the lateral aspect of the entire descending colon. The mucosal folds along the opposite wall are thickened but appear otherwise intact. Several serpiginous longitudinal ulcerations are faintly outlined extending throughout the transverse colon.

4*C*). The transverse linear ulcers may penetrate so deeply into the wall as to present in contour as numerous long thin spicules perpendicular to the long axis of the bowel (Fig. 4*B* and 8). These represent the deep fissures or fissure ulcers seen in gross specimens and may lead to small intramural abscesses or fistulae (Fig. 8). Internal fistulae are, however, less frequently seen than in granulomatous disease of the ileum. Perianal fistulae are quite common but rarely demonstrated on roentgen examination.

In contrast to granulomatous colitis, the early stages of ulcerative colitis show marked irritability and obliteration of the normal haustral pattern. The normal mucosal pattern is diffusely thickened and irregular but discrete areas of ulceration are difficult to recognize. Minute but diffuse ulceration is usually evident in contour as a fine irregularity of the margin. Eccentric localized intramural thickening and skip areas do not occur. Undermining of the mucosa, producing coarse irregular mucosal tags and bridges, is a characteristic feature in ulcerative colitis. Occasionally, minute intramucosal barium collections are seen which represent crypt abscesses in the colonic glands. These may be contrasted with larger submucosal or intramural abscesses seen in granulomatous disease. The picture of "burnt-out" ulcerative colitis with random sacculation or dilatation and irregular contractility of the colon has not been seen in granulomatous colitis.

Granulomatous colitis must be differentiated not only from ulcerative colitis but from several other conditions of the colon. This may be difficult when the area involved is single and limited in extent (Fig. 6). In such instances, diverticulitis or carcinoma of the colon or a foreign body perforation may be simulated. In diverticulitis, the mucosa is intact, diverticula are present, and a localized extrinsic mass due to abscess formation may be evident. In carcinoma, a rigid mass with elevated or overhanging edges is characteristic. Complete obstruction is rare in granulomatous disease of the colon despite the fact that short segments may become markedly narrowed.

SUMMARY

Granulomatous colitis may coexist with granulomatous disease of the small bowel (Crohn's disease) and in such instances presumably represents the same process. There are several types of coincident colonic disease which differ from each other essentially only in distribution.

Granulomatous colitis also exists as a primary condition confined to the colon. In such instances, identification with Crohn's disease is likely to be unproved. Previous designations of this condition which included terms such as "segmental" or "regional" should be discarded because it is now known that the entire colon may be involved and that the disease may be confined to the rectum and sigmoid. Differentiation from ulcerative colitis must be based at present on pathologic examination. However, there are roentgen features present in many instances, particularly early, which are highly suggestive of granulomatous colitis. These are described and illustrated.

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COLON LESIONS MASQUERADING AS SMALL BOWEL OBSTRUCTION ON THE PLAIN ROENTGENOGRAM OF THE ABDOMEN*

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THE roentgenographic findings in classic obstruction of the small and large intestine are well known and have been adequately described by many authors. The roentgen signs usually are diagnostic and often permit one to localize the site of obstruction. It is, however, not a matter of common knowledge that lesions of the colon may mimic small bowel obstructions on the plain roentgenogram of the abdomen. It is with this entity that we wish to concern ourselves by presenting a number of illustrative cases and by discussing the practical implications and the pathologic physiology involved. Hodges and Miller[2] have stated in referring to the roentgen examination in intestinal obstruction that when it is "employed alone it may be dangerously misleading." The chance for an erroneous diagnosis is manifest and misdirected surgery on the patient obvious unless the interpretation of the roentgenogram is tempered with a clinical history and the physical findings.

A typical colon obstruction is diagnosed by accumulation of gas and fecal material proximal to the lesion (Fig. 1, *A* and *B*). There may be concomitant small bowel distention. The important accepted fact is that the colon must be visualized. On the other hand, when there appears to be an abnormal distribution of air in the small bowel only, the observer is harldy prone to suspect a lesion elsewhere. It is here where

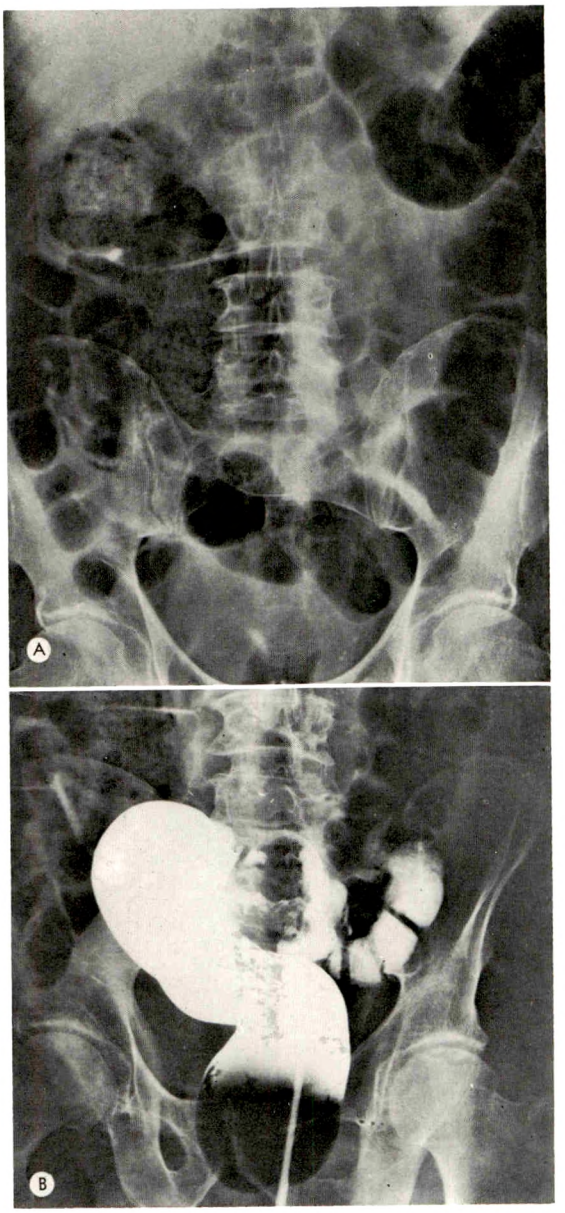


FIG. 1. (*A* and *B*) Typical colon obstruction. (*A*) A plain roentgenogram of the abdomen shows a large amount of fecal material in the right side of the colon. There is gas in the transverse colon, splenic flexure and descending colon. (*B*) Subsequent barium enema study shows a typical napkin-ring carcinoma of the rectosigmoid.

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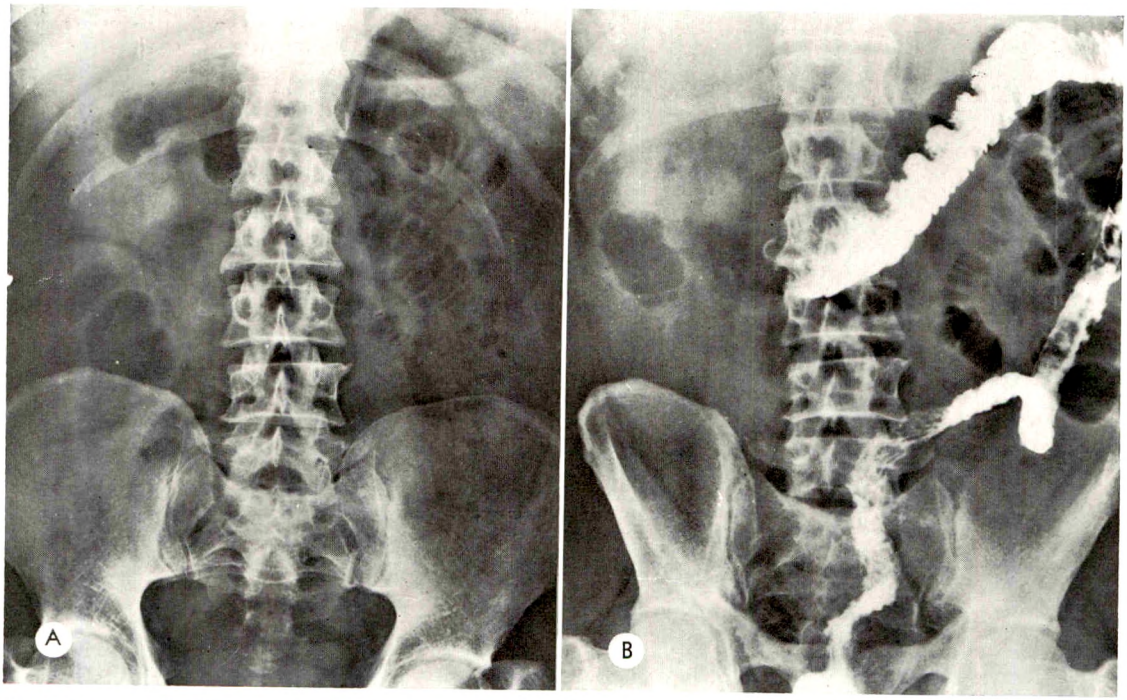


Fig. 2. (*A* and *B*) Carcinoma of transverse colon simulating small bowel obstruction. (*A*) A plain roentgenogram of the abdomen shows definite small bowel dilatation without any gas in the colon. A decubitus study revealed some fluid levels. These findings indicate a small bowel obstruction. (*B*) Barium enema study shows an obstruction in the transverse colon due to carcinoma.

clinical correlation becomes imperative. The ileum or jejunum or both may be markedly distended or there may be only a few scattered dilated segments. Sometimes there is seen only a single loop reminiscent of the "sentinel" loop described as a reflex phenomenon secondary to pathology elsewhere in the abdomen as may be seen in some cases of acute appendicitis, cholecystitis, pancreatitis, etc. It is incumbent to keep in mind that the colon either may appear empty and flaccid or may be visualized in normal fashion by a few pockets of gas or fecal material. Paralytic ileus hardly presents a problem because here normally both the colon and the small gut can be seen and the process can be inferred from the clinical history.

ILLUSTRATIVE CASES AND DISCUSSION

We have selected 6 illustrative cases to demonstrate our point. They are exemplified by Figures 2 through 6. The common denominator in all cases is the presence of simulated small bowel obstruction with the actual lesion being present in the colon. The etiologic entities in our material are neoplasm or diverticulitis. Over a period of many years we have been impressed with the pitfalls of misinterpreting the site of bowel obstruction from the scout roentgenogram of the abdomen. Ulin *et al.*,[6] in a study of 227 patients with acute large bowel obstruction due to carcinoma of the colon, noted with interest the presence of associated small bowel distention. In 40 per cent of their patients they found at least slight small bowel distention and in 20 per cent there was moderate to marked gaseous dilatation of the small bowel. Eight patients or 3.5 per cent of their series presented themselves "with historical and physical features leading to a clinical diagnosis (including radiography) of apparently pure small bowel obstruction on admission." Dennis[1] in 52 cases of large bowel obstruction describes an incidence of 5 per cent in which small bowel dilatation pre-

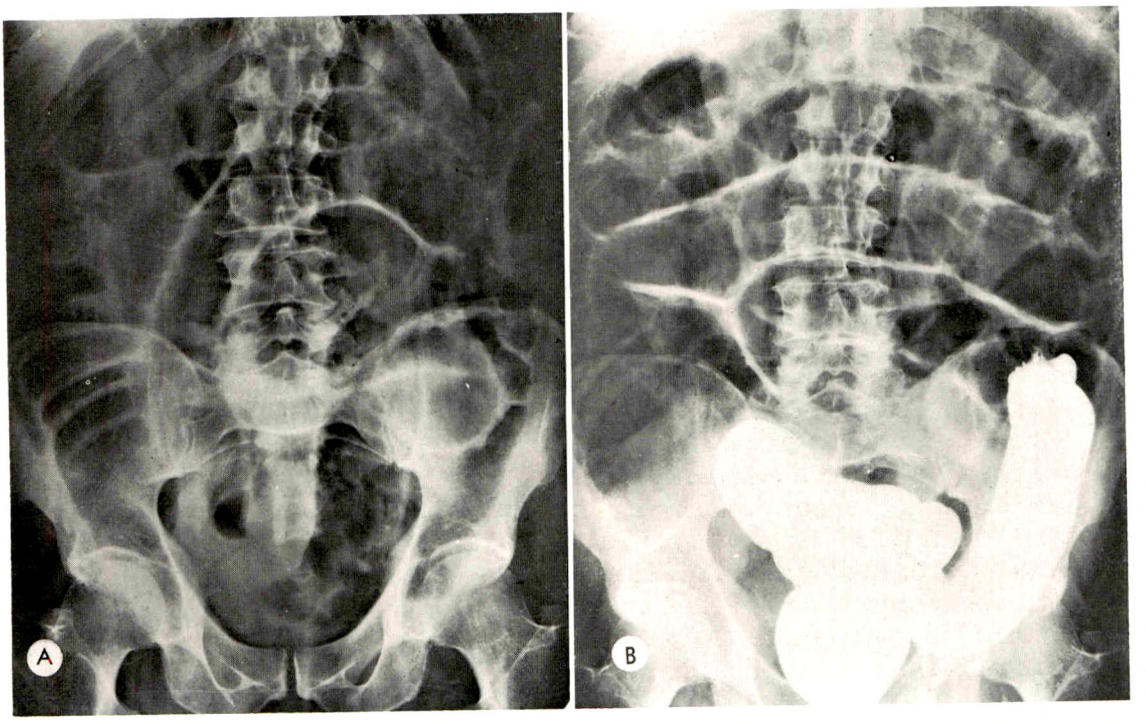


Fig. 3. (*A* and *B*) Carcinoma of mid-descending colon simulating small bowel obstruction. (*A*) A plain roentgenogram shows marked small bowel dilatation. (*B*) Barium enema study shows complete obstruction of the mid-descending colon by carcinoma. Typical step ladder arrangement of small intestinal loops remain a feature. The cecum is outlined by gas but otherwise the colon in no way reflects the large bowel obstruction.

dominated. Levitin[3] states that a carcinoma will cause distention of the bowel proximal to the obstruction and sometimes of the small intestine. The appearance of the latter then is that of a mechanical obstruction.

The mechanism of the presence of gas in the small bowel in cases of colon obstruction has been under much discussion and speculation. Normally, approximately 68 per cent of gas in the gut is derived from swallowed air and only 32 per cent originates locally by diffusion from the blood into the intestinal lumen or by putrefactive activity of the intestinal bacteria. There are divergent opinions regarding the competency of the ileocecal valve in explaining the small bowel distention in obstructing colon lesions. Ulin *et al.*[6] believe that the valve is rarely incompetent and quote evidence to the effect that the material in the obstructed colon segment is not derived from putrefaction and secretion. They express doubt that the obstructed colon generates gas and fluid to a pressure large enough to force open the ileocecal valve. Conversely, Love,[4] in an excellent discussion on the role of the ileocecal valve in large bowel obstruction, presents evidence in support of the thesis of incompetence. He bases his conclusion on the experimental findings of Rendlemen *et al.*[5] and Dennis.[1] The former measured pressures during enema examinations to overcome resistance of the ileocecal valve and found reflux in 20 per cent of the patients at pressures of 20 cm. of water or below, in 36 per cent at 25 cm. or below, in 84 per cent at 50 cm. or below and in 96 per cent at 90 cm. or less. The intraluminal pressure in 34 cases of large bowel obstruction at the site of the transverse colostomy was measured by Dennis. It was 14 cm. on average and the highest recorded was 34 cm. of water. From these data Love[4] con-

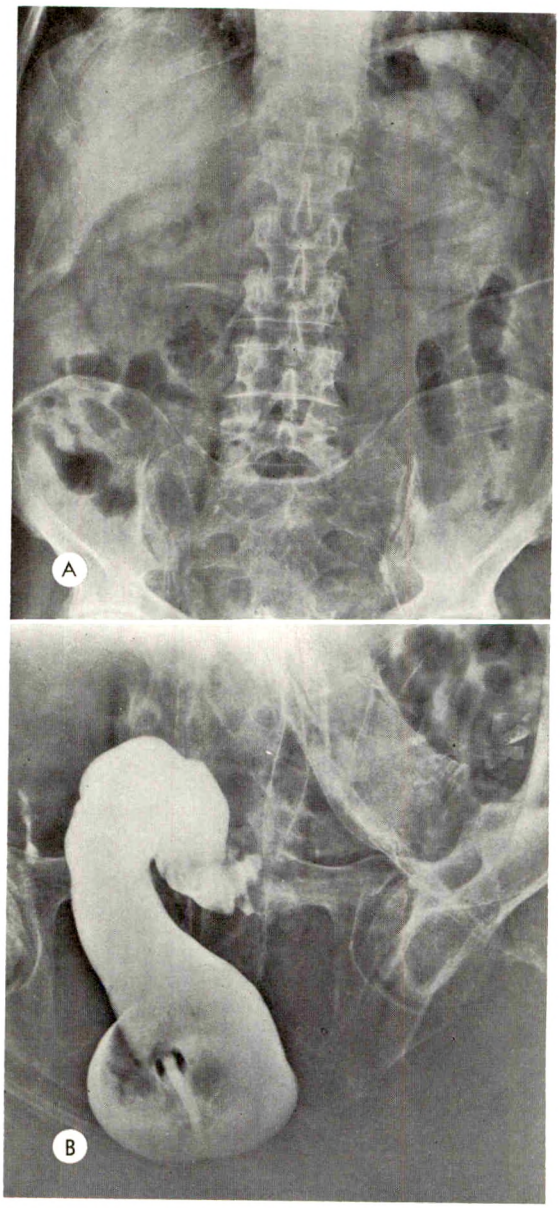


FIG. 4. (*A* and *B*) Carcinoma of the rectosigmoid simulating small bowel obstruction. (*A*) A scout roentgenogram shows a few scattered loops of dilated small bowel. No discernible gas or fecal material is noted in the colon. The findings are suggestive of early small bowel obstruction or ileus. (*B*) Barium enema study shows a complete sigmoid obstruction without backing up of gas or fecal material in the remainder of the colon.

cludes that the ileocecal valve will yield to intracolonic pressure in obstruction in 30 per cent of patients. Every radiologist is familiar with the varying degree of patency of the ileocecal valve and there is a majority opinion that incompetency does exist. We believe that it is a major factor to account for the paradox of an apparent small bowel obstruction in the presence of actual colon obstruction. It is somewhat difficult, however, to explain this phenomenon alone as the result of a patent ileocecal valve. If such were the case, there should be an attending dilatation of the colon proximal to the obstruction as well. It would appear more likely that the colon has emptied its gaseous content into the small intestine by reverse peristalsis activated by the pathologic process. Another plausible cause is reflex ileus. Finally, there may be an actual small bowel obstruction coexistent with a colon lesion as shown by our case demonstrated in Figure 6, *A* and *B*. A perforated diverticulum and diverticulitis or perforated carcinoma with abscess formation frequently result in complete mechanical obstruction of the small intestine. This takes place when the small intestine becomes adherent or occluded by extrinsic invasion. In mechanical obstruction of the small bowel produced by, but secondary to, a colon lesion, immediate surgery is mandatory; whereas, if the obstructing lesion is in the colon and is only mimicking small bowel distention on the flat roentgenogram of the abdomen, decompression, proper preparation of the bowel and supportive treatment may allow definitive surgery at the first operation.

The purpose of this discussion is to alert the surgeon, clinician and radiologist to the possibility of erroneously diagnosing a small bowel obstruction when the offending lesion is in the colon. The answer, of course, lies in performing a barium enema examination after taking into account the history and the physical findings rather than relying on the interpretation of the scout roentgenogram alone.

SUMMARY AND CONCLUSIONS

1. Colon lesions masquerading as small

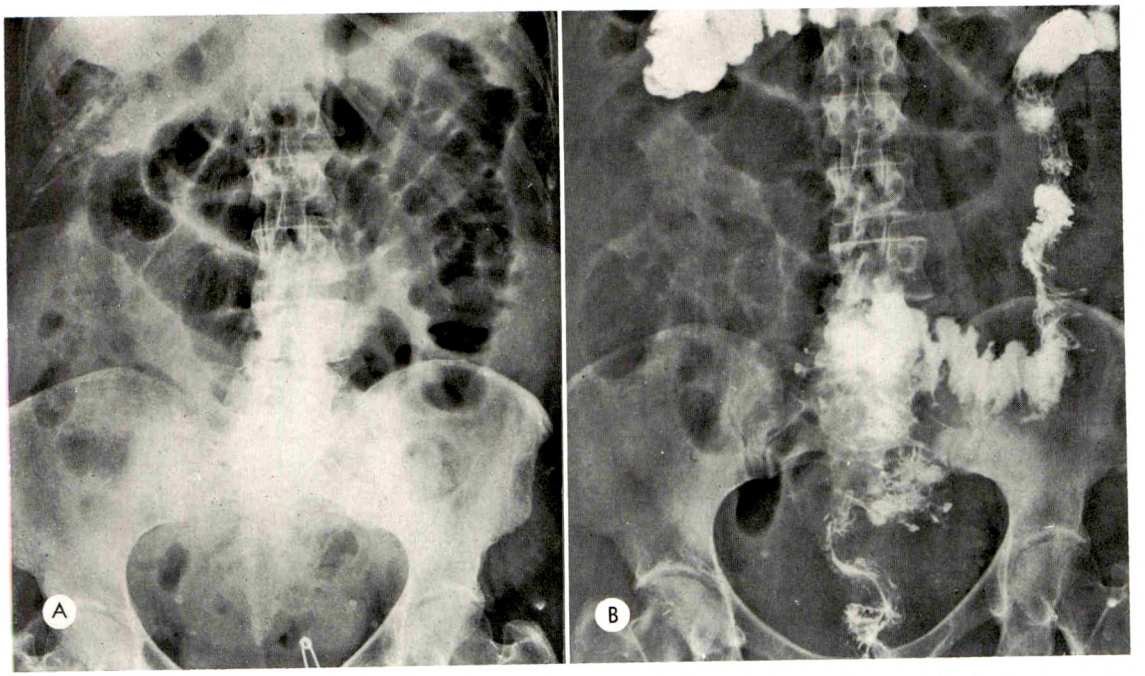


Fig. 5. (*A* and *B*) Severe sigmoid diverticulitis simulating small bowel obstruction. (*A*) Preliminary roentgenogram of the abdomen shows dilated loops of small bowel with practically no gas in the colon. Some fecal material is observed in the ascending portion. The immediate impression is small bowel obstruction. (*B*) Barium enema study reveals a severe obstructing diverticulitis of the sigmoid.

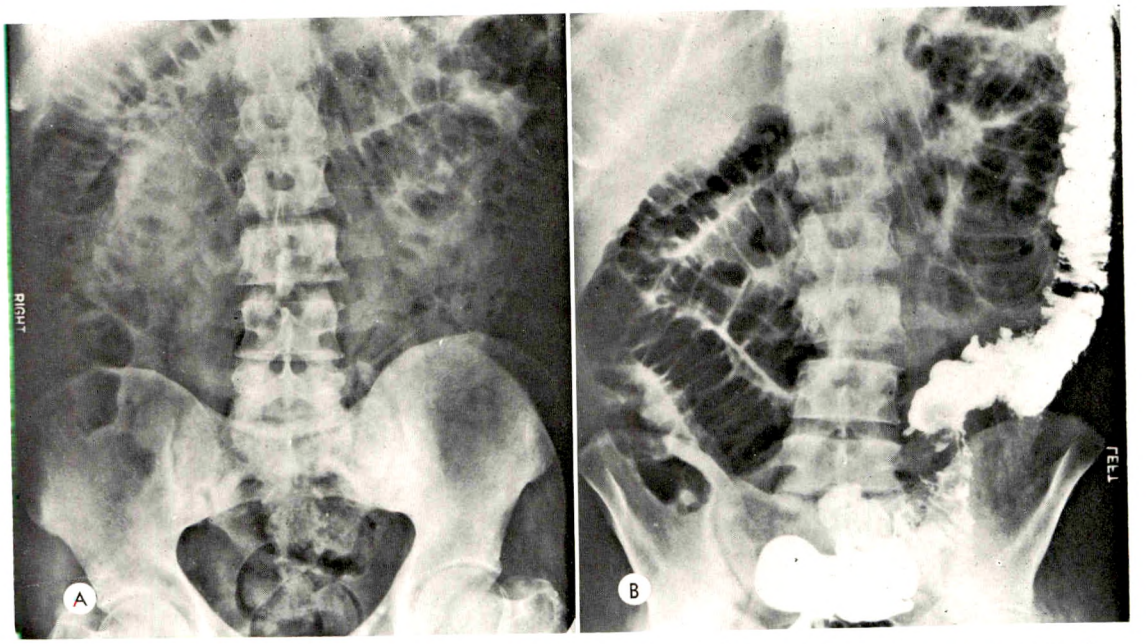


Fig. 6. (*A* and *B*) Obstruction of sigmoid colon secondary to diverticulitis and abscess formation and mechanical small bowel obstruction due to adhesions to sigmoid mass. (*A*) A plain roentgenogram of the abdomen shows dilated loops of small bowel with practically no gas nor feces in the colon except in the rectum. This roentgenogram alone would suggest a small intestinal obstruction. (*B*) Subsequent barium enema study reveals a severe obstructing diverticulitis in the sigmoid.

bowel obstruction on the scout roentgenogram of the abdomen are documented by illustrative carcinoma and diverticulitis cases.

2. The mechanism of small bowel distention in the presence of a flaccid colon harboring an obstructing lesion is discussed. The most common causes are incompetency of the ileocecal valve, reverse peristalsis due to irritability from the lesion, reflex ileus and associated mechanical small bowel obstruction by adhesions or direct invasion.

3. Correlation with clinical and physical findings should initiate a barium enema study and thus obviate an erroneous diagnosis based on the interpretation of the scout roentgenogram of the abdomen alone. Accurate diagnosis may eliminate multiple surgical procedures.

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FLUID-FILLED LOOPS IN INTESTINAL OBSTRUCTION*

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THE roentgen diagnosis of intestinal obstruction is usually based upon the appearance and distribution of abnormal quantities of gas in the abdomen. In some cases of obstruction, however, little or no gas is present, and the loops are filled only with fluid. These fluid-filled obstructions present an atypical picture, and the diagnosis is often missed by both the clinician and radiologist.

Frimann-Dahl[3] in 1944 first described 12 cases of intestinal obstruction in which the loops contained little or no gas. In all his cases the intestine was strangulated at the time of surgery. Since 1944 numerous American workers have described fluid-filled loops in cases of strangulating obstructions of the small intestine.[2,8,10,11,13] These have been called "pseudotumors" because of the homogeneous shadow of water density cast by the fluid-filled loops, and they have been considered to represent evidence of strangulation of the small intestine. No author, however, has emphasized that simple nonstrangulating obstructions of both the small intestine and the colon may also show fluid-filled loops which contain little or no gas.

We have reviewed the roentgenograms of 300 cases of obstruction of the small intestine and have found fluid-filled loops with little or no gas in 18 patients, an incidence of 6 per cent. In 6 of these 18 patients, the amount of gas was so small that it could not be readily appreciated on a supine roentgenogram although it was usually visible on erect or decubitus films. In 12 of the 18 patients with fluid-filled loops, there was no evidence of strangulation of the obstructed intestine at the time of surgery.

The contents of an obstructed intestine consist of fluid alone or fluid and gas in varying amounts, but the proportion each contributes to abdominal distention varies with the individual. If no gas is present there may be little or no clinical evidence of abdominal distention. In this series of 18 patients with fluid-filled loops the abdomen was not distended in 6 cases, while an additional 4 patients had questionable or only slight distention. Thus in over one-half of the patients this important clinical sign of intestinal obstruction was absent or equivocal (Table 1).

Increased peristaltic sounds occurring simultaneously with colicky pain represent another important clinical sign of intestinal obstruction. In patients with fluid-filled loops and little or no gas, the peristaltic sounds may be normal or diminished because there are no gas bubbles to gurgle. In this series of 18 cases, the peristaltic sounds were classified as being increased in 7 patients and questionably increased in 3 patients. In 8 individuals the sounds were considered to be normal or diminished (Table 1).

In the absence of abdominal distention and increased peristaltic sounds, the diagnosis is often not obvious clinically. In these cases the role of the roentgenologist is of great importance.

ROENTGEN DIAGNOSIS

The roentgen diagnosis of fluid-filled loops may be very difficult when little or no gas is present. Wangensteen[13] has suggested that pneumoperitoneum may be of value in questionable cases. We have not found it necessary to resort to this tech-

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Presented at the Sixty-second Annual Meeting of the American Roentgen Ray Society, Miami Beach, Florida, September 26–29, 1961.

Table I

	Age and Sex	Type of Pain	Abdominal Distention	Peristaltic Sounds	Anatomic Diagnosis
Nonstrangulated small intestine	73 ♀	Colicky	○	N	Incarcerated incisional hernia
	57 ♂	Colicky	±	↑	Obstructed ileum due to adhesions
	86 ♀	Colicky	+	↑	Obstructed ileum due to adhesions
	71 ♂	Colicky	±	↑?	Obstructed jejunum due to adhesions
	49 ♀	Colicky	○	N	Richter's hernia
	73 ♀	Colicky	○	N	Obstructed ileum due to adhesions
	59 ♀	Colicky	○	↑	Gallstone ileus
	43 ♂	Colicky	+	↑	Obstructed ileum due to adhesions
	53 ♀	Colicky	+	↑?	Obstructed ileum due to carcinoma of ovary
	55 ♀	Colicky	±	↑	Obstructed ileum due to regional enteritis
	68 ♀	Colicky	±	↑?	Femoral hernia
	53 ♂	Colicky	+	↑	Obstructed ileum due to adhesions
Strangulated small intestine	22 ♂	Constant	○	N	Volvulus of ileum due to adhesions
	39 ♂	Colicky	○	↑	Volvulus of jejunum
	69 ♂	Colicky	+	N	Richter's hernia
	63 ♂	Colicky	+	↓	Volvulus of ileum due to adhesions
	64 ♀	Constant	+	↓	Volvulus of jejunum due to adhesions
	78 ♀	Colicky	+	↓	Obstructed ileum due to adhesions

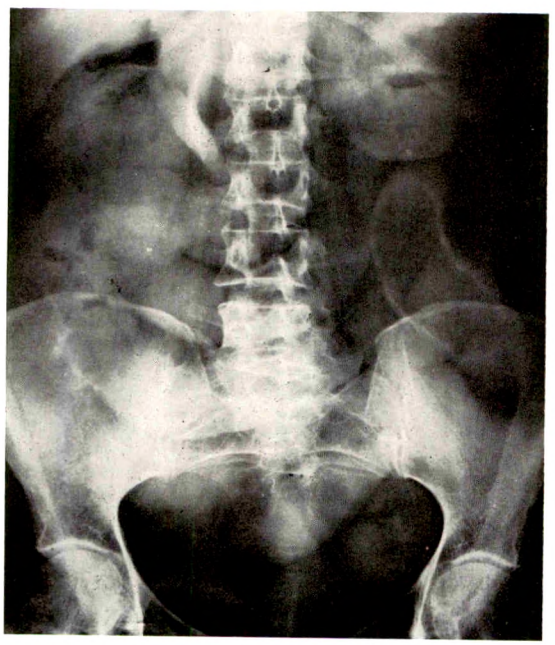


Fig. 1. Obstructing Richter's hernia in a patient who had a therapeutic pneumoperitoneum for pulmonary tuberculosis. On this supine roentgenogram the fluid-filled loops are easily visible because they are partially surrounded by free intraperitoneal air.

nique but it would obviously be effective (Fig. 1).

On plain roentgenograms of the abdomen, the diagnosis of fluid-filled obstructions depends upon (1) evidence of stretching of the valvulae conniventes in the jejunum or proximal ileum (positive stretch sign) and (2) recognition of soft-tissue densities caused by the fluid-filled loops. Stretched valvulae conniventes may be readily diagnosed by opaque medium or by the characteristic appearance of small amounts of gas. Two of our patients had taken opaque self-medication (probably bismuth compounds) for nausea and vomiting prior to hospital admission. In both cases the opaque granules lined up against the stretched valvulae conniventes and appeared as a series of parallel streaks (Fig. 2, *A* and *B;* and 3*A*). We have called this appearance a "positive stretch sign." It is not seen in the normal intestine and is apparently a reliable indication of dilated gut.

If there is a small amount of gas in the obstructed intestine, the contour of the gas

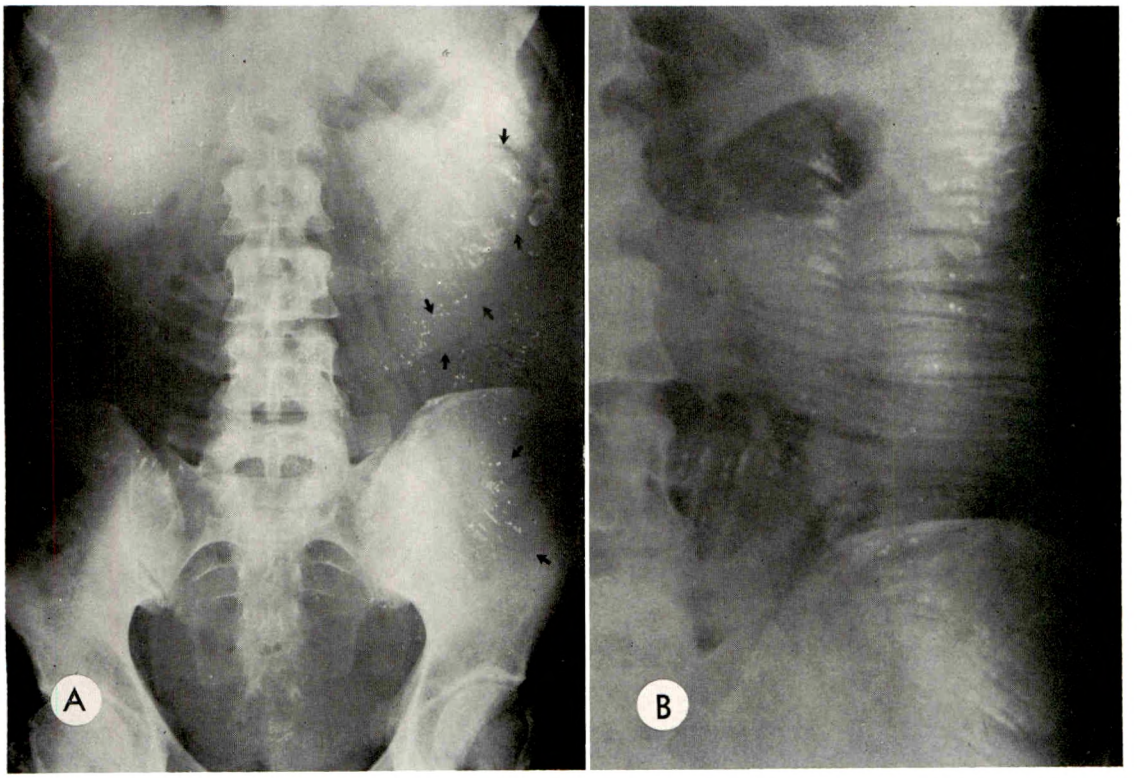


Fig. 2. Obstruction of distal ileum secondary to adhesions. (*A*) The linear distribution of granules of opaque self-medication indicates stretched valvulae conniventes (positive stretch sign) and is diagnostic of fluid-filled loops. Arrows point to obstructed loops. (*B*) Supine roentgenogram after 50 cc. of oral barium. The obstructed loops are faintly opacified. The opaque granules of medication are lined up between the radiolucent stretched valvulae conniventes.

is usually different from gas collections in a nonobstructed intestine and is usually diagnostic of a fluid-filled loop. When the patient is in either the erect or the decubitus position, the gas separates into a series of small bubbles (Fig. 3*B;* and 4*C*). This appearance has been noted by Frimann-Dahl,[6] who described it as an oblique string of beads. This series of small gas bubbles is common in the obstructed intestine and is due to the trapping of gas beneath the stretched valvulae conniventes. This is another manifestation of a "positive stretch sign."

When the patient is in the supine position, a small amount of gas appears as a series of thin parallel radiolucencies. These gas streaks represent a third manifestation of a "positive stretch sign" and are considered to be reliable evidence of dilated intestine (Fig. 4*B*). In a nonobstructed intestine a small amount of gas would appear as circular, oval, or squarish radiolucencies rather than as thin parallel streaks.

When no gas is visible in the obstructed intestine, the only way the correct diagnosis can be made is to note the subtle contours of soft-tissue masses. If such shadows are unexplained and cannot be palpated, they must cause one to suspect fluid-filled loops if the patient has symptoms compatible with an intestinal obstruction. In some instances there is a polycyclic or scalloped border but this is not invariable, and the group of obstructed fluid-filled loops may have a smooth contour resembling an ovarian cyst, distended bladder, perinephric abscess, etc. Erect or decubitus roentgenograms are often of value in de-

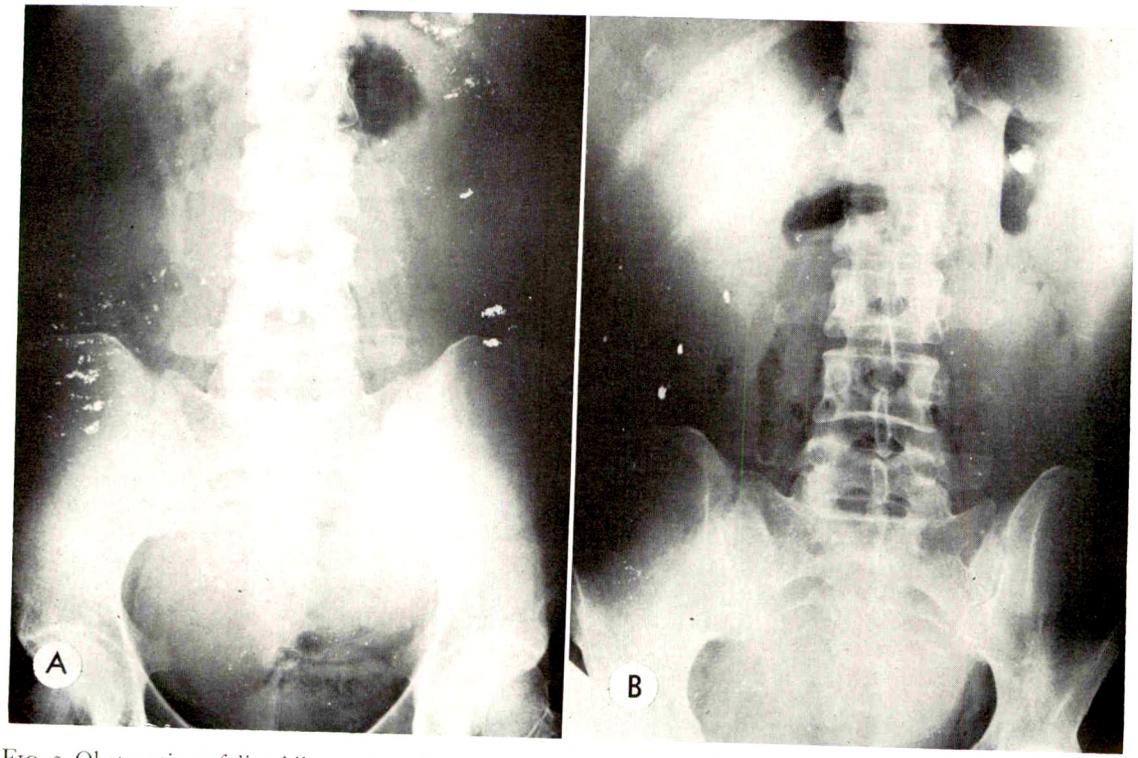


Fig. 3. Obstruction of distal ileum secondary to adhesions. (*A*) Supine roentgenogram. The nonpalpable soft-tissue densities in the lower abdomen and the distribution of opaque medication (positive stretch sign) suggest dilated fluid-filled intestine. (*B*) Decubitus roentgenogram with left side up. The oblique string of gas bubbles in the left flank is due to gas trapped beneath stretched valvulae conniventes. This constitutes a positive stretch sign and is a reliable indication of dilated intestine. The air-fluid level is in the stomach.

termining the nature of the unexplained soft-tissue densities because if they are due to fluid-filled loops the change in position may cause one of the loops to turn on end, and it is then easily visible as a circular soft-tissue density. If considerable mesenteric fat is present, it is usually possible to delineate the individual fluid-filled loops. Contrast may be enhanced by taking a lateral roentgenogram of the abdomen with the patient lying on either the right or left side. With this technique there is a greater proportion of fat to contrast with the fluid-filled loops which lie in the anterior part of the abdomen (Fig. 5, *A* and *B*).

Strangulated Small Intestine

In one-third of our small intestinal obstructions with little or no gas, there was strangulation of the intestine at the time of surgery. If one sees a soft-tissue density (pseudotumor) with gaseous distention of the intestine proximal to it, the chances are very great that the pseudotumor represents gangrenous gut.[4,8,10] When there is little or no gas proximal to the soft-tissue density, it is not possible to differentiate between strangulating and nonstrangulating types of obstruction (Fig. 6).

Correlation of the clinical history, physical findings, and roentgenograms is very important when the diagnosis of intestinal obstruction is not obvious. The patient whose roentgenogram is shown in Figure 7 had a sudden onset of constant upper abdominal pain, with nausea and vomiting, 4 hours prior to this roentgenogram. There was tenderness and resistance in the left upper abdomen corresponding to the nonpalpable soft-tissue density. The correlation of the history, roentgenograms, and physical findings suggested that the mass

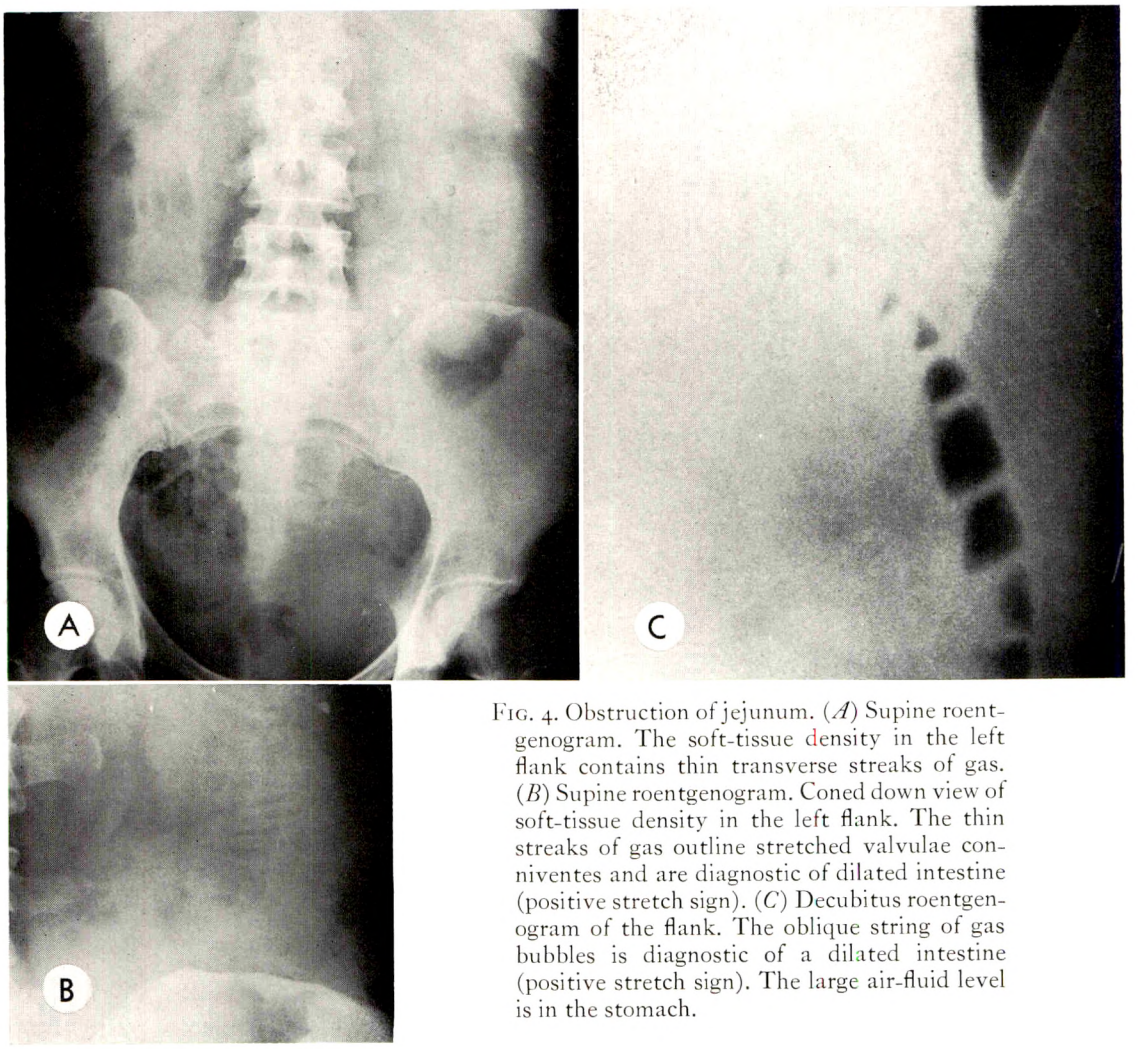


Fig. 4. Obstruction of jejunum. (*A*) Supine roentgenogram. The soft-tissue density in the left flank contains thin transverse streaks of gas. (*B*) Supine roentgenogram. Coned down view of soft-tissue density in the left flank. The thin streaks of gas outline stretched valvulae conniventes and are diagnostic of dilated intestine (positive stretch sign). (*C*) Decubitus roentgenogram of the flank. The oblique string of gas bubbles is diagnostic of a dilated intestine (positive stretch sign). The large air-fluid level is in the stomach.

was due to obstructed fluid-filled loops because an intraperitoneal tumor as large as this one should have been easily palpable. The sudden onset of symptoms and the constant pain are features which suggest strangulation.[11] Immediate surgery was performed and 70 cm. of gangrenous jejunum due to a volvulus was removed.

In one patient, seen at Presbyterian Hospital, New York, New York, the correct diagnosis was made only because the author saw the patient and was impressed with her apparent stoical disposition. Patients with this personality trait, as will be noted later, tend to swallow little air and to have fluid-filled obstructions. With this in mind the roentgenogram was re-examined and the fluid-filled loops were seen in the left flank (Fig. 8). Immediate surgery was performed and this proved to be a volvulus of the jejunum. The intestine was markedly discolored but resection was not necessary, so that this should be classified as incipient gangrene. If this roentgenogram had been considered negative, there is little doubt that surgery would have been delayed until frank gangrene was present.

COLON OBSTRUCTIONS

Fluid-filled loops can also occur in obstructions of the colon. We have seen 3 cases. Figure 9*A*, a supine roentgenogram

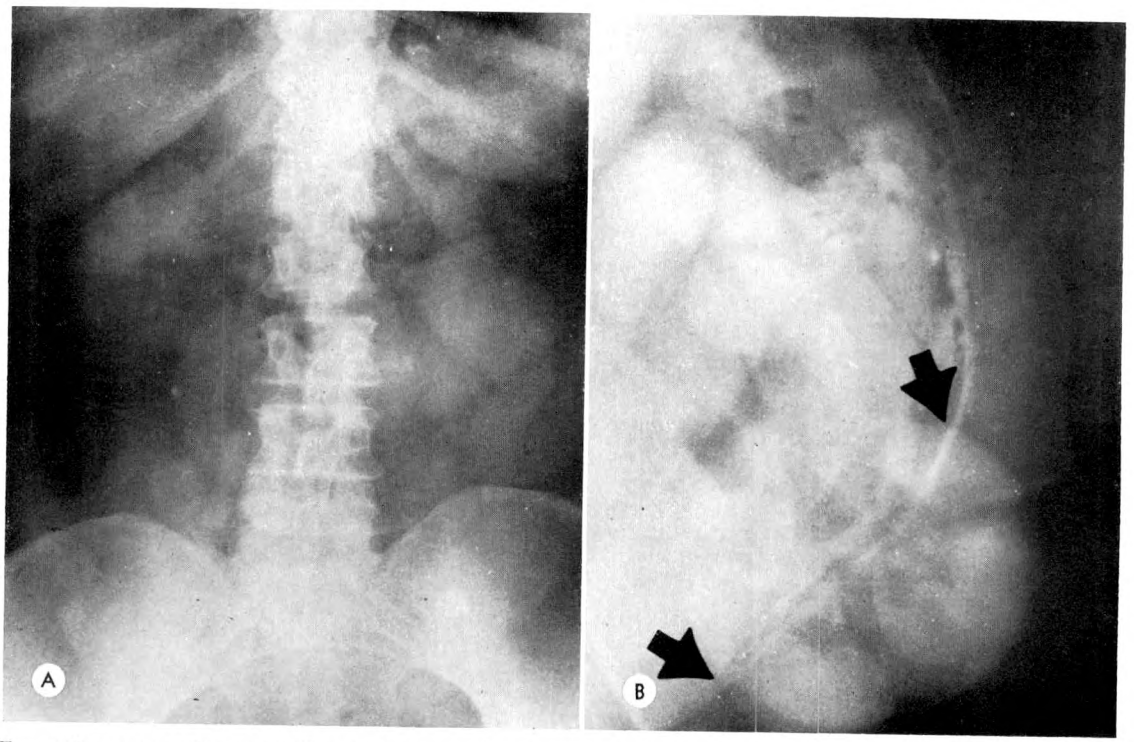
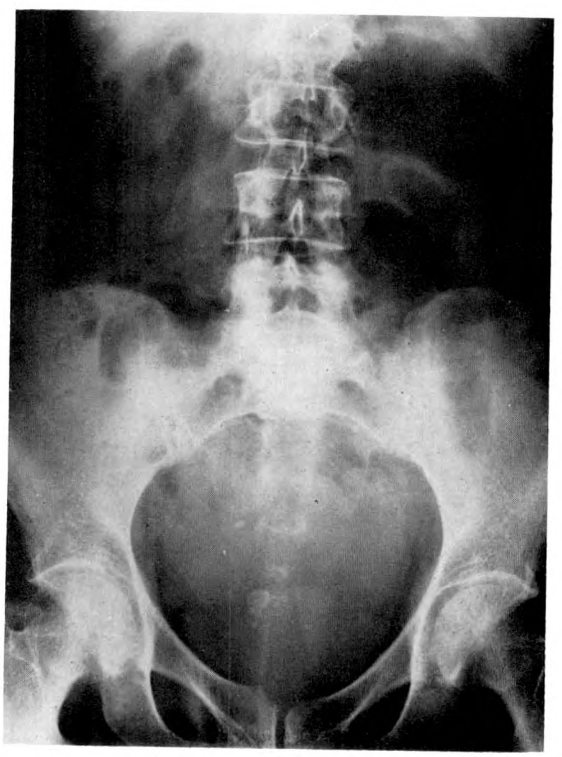


Fig. 5. Incarcerated incisional hernia in a very obese woman. (*A*) Supine roentgenogram. Fluid-filled loops are visible in the left flank but in a patient of this size they are difficult to differentiate from skin folds. (*B*) Lateral roentgenogram of the anterior half of the abdomen. The fluid-filled loops are clearly visible because they are contrasted with fat. One loop extends through the peritoneum at arrows.



of the abdomen, could very readily be classified as negative or might suggest ascites. There is no visible gas except a small bubble in the stomach. Fortunately, the clinical diagnosis on this patient was small intestinal obstruction so that an erect roentgenogram was available. In the erect position (Fig. 9*B*) the diagnosis of an obstruction or a paralytic ileus is obvious. The short air-fluid levels call attention to the markedly distended intestinal loops. One might guess that this is a small intestinal obstruction, but we have learned from our 3 cases that it is not possible to differentiate between a colon occlusion and

Fig. 6. Gangrenous ileum (95 cm.). Supine roentgenogram. There is a nonpalpable soft-tissue density in the pelvis. Catheterization excluded a distended bladder. The strangulated obstruction was due to adhesions.

a low small intestinal obstruction when fluid-filled loops are visible throughout the abdomen. An emergency barium enema examination is the diagnostic procedure of choice in these patients.

DISCUSSION

Patients with fluid-filled obstructions usually have nausea, vomiting, and pain, but there is often little or no abdominal distention because there is no gas to help dilate the gut. If no gas is present the clinician will not hear increased peristaltic sounds because there are no gas bubbles to gurgle. In such cases the correct diagnosis is often not obvious clinically, and this makes the correct interpretation of the roentgenograms even more crucial. The referring physician may well request only a supine roentgenogram of the abdomen, and this will lead to an increased incidence of error by the radiologist because in many cases the correct diagnosis is easily made on erect or decubitus roentgenograms, whereas it might not be suspected on a single supine film. Erect or lateral decubitus roentgenogram of the abdomen should be taken if there is any clinical suspicion of an intestinal obstruction. This policy has often been of value, particularly in these fluid-filled obstructions.

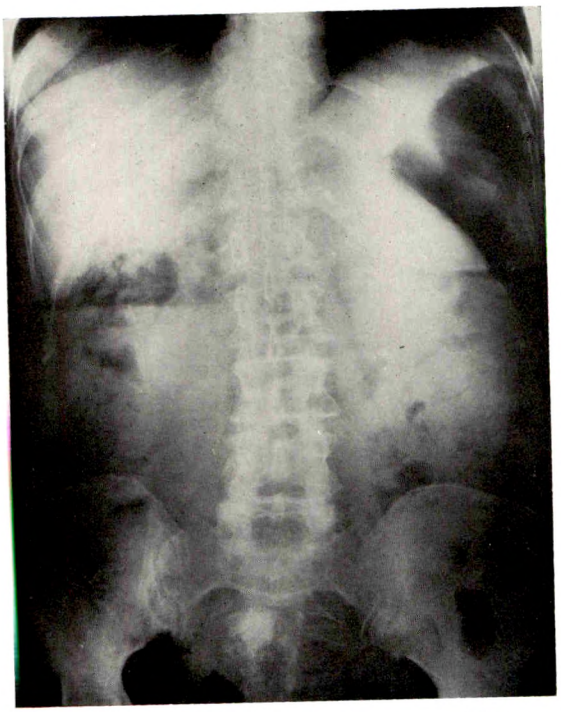


Fig. 7. Volvulus with 70 cm. of gangrenous jejunum. Supine roentgenogram. Fluid-filled loops appear as a smooth left upper quadrant mass which displaces the gastric air bubble. There was no gas in the obstructed loops on decubitus roentgenograms.

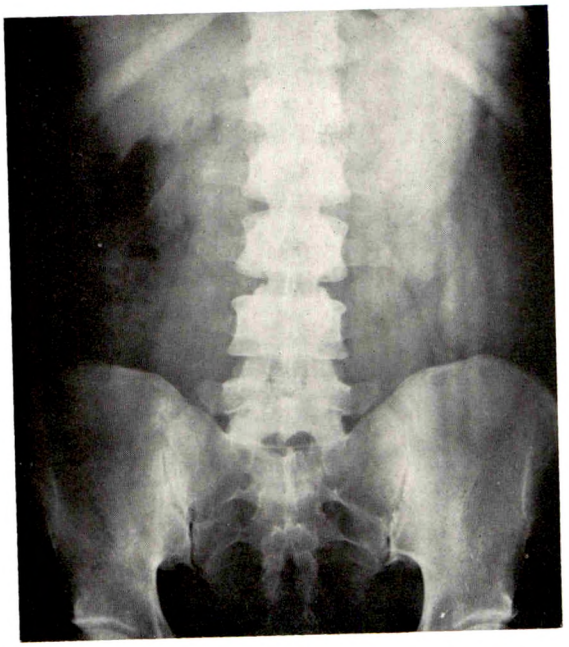


Fig. 8. Volvulus of the jejunum with incipient gangrene. Fluid-filled loops are visible in the left flank. There was no gas in the obstructed intestine. (From Presbyterian Hospital, New York, New York.)

Why some obstructions contain gas and others contain none is a matter of great interest. It now appears to be well established, both clinically and experimentally, that little or no gas is formed in the obstructed intestine.[1,6] The only gas that is present in sufficient quantity to be of much value to the radiologist is gas that has been swallowed, and it would appear that patients with fluid-filled nonstrangulating obstructions tend to swallow little or no air. In many cases we have attempted to correlate personality type with the presence or absence of gas in the intestine. The patients with fluid-filled obstructions have tended to appear stoical, whereas patients who moan, groan, grunt, complain of pain, or

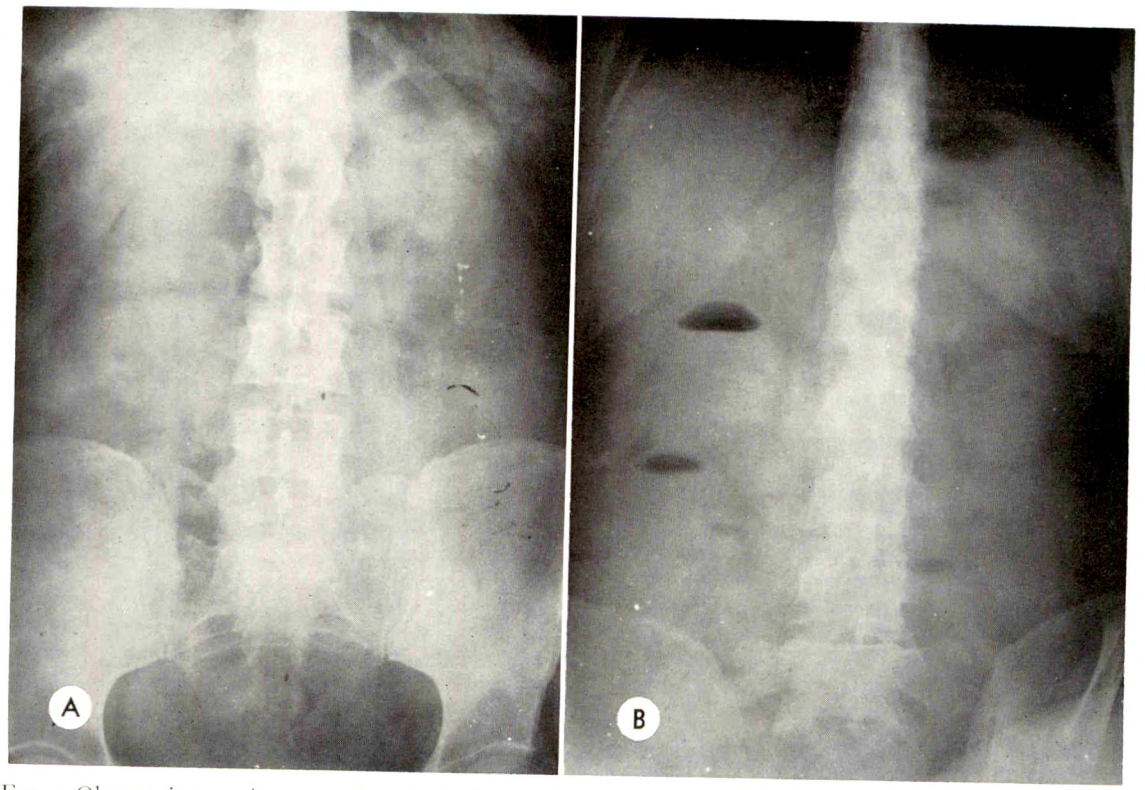


FIG. 9. Obstructing carcinoma at the splenic flexure of the colon. (*A*) Supine roentgenogram. The diffuse increase in density is due to obstructed fluid-filled loops but there is no clue as to the exact site of obstruction. (*B*) Erect roentgenogram. The short air-fluid levels call attention to markedly distended intestinal loops.

swallow constantly have usually had gaseous distention of the obstructed intestine. Two women were typical of the group with fluid-filled loops. Both showed no significant emotion over their illness. On questioning, they admitted to having pain and, in a very matter-of-fact tone, described it as "similar to labor pains but maybe a little worse." In one of these patients, as was mentioned previously, the correct roentgen diagnosis was made only because the radiologist saw the patient and was impressed with her stoical disposition. The abdominal roentgenogram was then re-examined and the very subtle fluid-filled loops were seen. The only common denominator we have found in patients with nonstrangulated fluid-filled loops appears to be a stoical personality type. When strangulation is present, however, there may be considerable paralysis of the intestine proximal to the occlusion, so that even if the patient swallows some air it will not readily pass into the intestine due to this paralysis and may finally be vomited. This might explain why patients with strangulating obstructions and mesenteric thromboses tend to accumulate less gas than patients with simple obstructions.

The high incidence of gangrene in fluid-filled loops is both interesting and important. It occurred in 33 per cent of our series of small intestinal obstructions, but it was present in all 12 cases described by Frimann-Dahl,[3] and gangrene has been present in practically all the other cases of fluid-filled loops described in the literature. We have not found any clue on the roentgenograms which would help us differentiate between simple obstructions and strangulating obstructions when there is little or no gas within the fluid-filled loops or proximal to them. It would appear, therefore, that in the absence of gas the

diagnosis of strangulating obstruction must be made clinically, and that the roentgenologist can only say that the incidence of gangrene is probably higher in patients with fluid-filled obstructions than it is when there is gaseous distention. In this series of 300 cases of small intestinal obstruction, the only reliable indications of strangulation were a history of a sudden onset of pain or the presence of constant abdominal pain in a patient who had a definite intestinal obstruction. All other so-called signs of strangulation such as leukocytosis, high fever, rapid pulse, shock, abdominal rigidity, tenderness, etc. proved to be unreliable on more than one occasion.

One might suspect that fluid-filled obstructions represent early cases in which gas has not had time to accumulate. This is not so since only 5 of our 18 patients had symptoms for less than 12 hours at the time of admission. In half of our patients symptoms had been present for 3 days or more at the time of admission, so that these tend to be late obstructions rather than early ones. Obstructions with vascular compromise may cause severe symptoms earlier than do simple obstructions, but as was pointed out by Frimann-Dahl[3] and Reinus[11] positive roentgen findings tend to appear later in strangulating obstructions than they do in simple obstructions.

It is apparent that all unexplained soft-tissue shadows do not represent obstructed fluid-filled loops. It should be emphasized, however, that any unexplained soft-tissue density which cannot be palpated should make one suspect fluid-filled loops if the patient's symptoms are compatible with an obstruction. If there is any reasonable doubt about the diagnosis, it is perfectly simple to give 50 cc. of barium orally and then obtain a roentgenogram after the patient has been on his or her right side for a short time. Our experience agrees with that of Frimann-Dahl[5] that this simple technique is safe, is perfectly adequate for the purpose, and does not interfere with the handling or treatment of these acutely ill patients.

SUMMARY

In 6 per cent of small intestinal obstructions and in occasional obstructions of the colon, the loops are filled with fluid but little or no gas is present.

The incidence of strangulation is higher in patients with fluid-filled obstructions than it is when there is gaseous distention.

The lack of gas in nonstrangulating obstructions appears to be correlated with patients who have a stoical personality and apparently swallow little or no air. In strangulating obstructions, on the other hand, it is possible that paralysis of the intestine and excessive vomiting may contribute to the lack of gas.

The diagnosis of fluid-filled obstructions may present difficulty to both the clinician and the radiologist. The clinical picture may be confusing when there is no evidence of either abdominal distention or increased peristaltic sounds. In these cases the correct diagnosis may depend solely on accurate roentgen interpretation. In other cases, however, the clinician may well suspect the correct diagnosis, but he will be misled and treatment will be delayed if the radiologist fails to confirm the diagnosis by looking for and identifying the fluid-filled loops.

Barium by mouth is indicated if there is any doubt about the diagnosis. This is a safe procedure.

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SCLERODERMA OF THE SMALL BOWEL*

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THE protean manifestations of scleroderma, or progressive systemic sclerosis, have been described in the medical literature. Very little, however, has been reported regarding the distribution of the roentgenographic small bowel changes in this disease.

Rake's article[24] in 1931 probably contains the earliest mention of abnormal small bowel roentgen findings. In 1944, Hale and Schatzki[13] described 4 cases out of 18 in which abnormal small bowel patterns were found in patients with scleroderma. By 1954, Abrams, Carnes, and Eaton[1] were able to report 21 cases. Six of these cases had been discovered at their institution. Also in 1954, Boyd, Patrick, and Reeves[4] of Duke Hospital, reviewing cases of scleroderma from the roentgenographic aspect, reported only 4 patients with abnormal small bowel studies. Rosenthal[25] added one more case, bringing the total number of cases to 26. In 1959, Sommerville, Bargen, and Pugh[30] reported 11 cases with roentgenologic changes in the small intestine. Gondos[12] reported on 25 cases of scleroderma, 15 of which had small bowel studies, and 3 (20 per cent) were found to have abnormal roentgenograms. In September, 1961, Tuffanelli and Winkelmann[32] of Mayo Clinic added 4 cases to the literature, which brings the total number of reported cases to 44. The present report deals with 23 more cases from our institution, bringing the total to 67.

MATERIAL

From 1930 to 1960, 191 cases of scleroderma have been seen at Duke University Hospital. The usual ratio of female to male was present as was the usual age distribution. Of this group of patients, we were able to find gastrointestinal tract roentgenograms of 92 (48 per cent) (Table I). Forty (43 per cent) had esophageal studies only, while 52 (57 per cent) had studies of the esophagus, stomach, and small bowel. After reviewing these 52 studies, we felt that 23 (44 per cent) showed abnormal small bowel patterns. These 23 cases constitute 12 per cent of our total cases; the next closest series with an adequate number of cases with which to compare incidence is the Mayo group with 2.05 per cent of their patients showing abnormal small bowel studies.

TABLE I

CASES OF SCLERODERMA

Total No.	Esophageal Study Only	Esophagus and Small Bowel Study
191	40	52

Cases with Small Bowel Studies	Abnormal Small Bowels
52	23

ROENTGENOLOGIC FINDINGS

We have noted the following roentgenologic changes (Table II). The duodenal bulb and loop were found to be dilated and retained barium after the stomach was empty, the duodenal bulb retaining the barium as long as 24 hours after ingestion. Eleven of the cases retained the barium in the loop and 7 in the bulb. We found one other unusual phenomenon in 5 of the cases. In the transverse portion of the duodenum, usually 1 to 3 cm. beyond the flexure, there was a rather sharp, smooth, shelving margin which extended obliquely

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downward and slightly laterally. We believe that this is merely a manifestation of the pressure effect from the superior mesenteric artery on the stiffened and thickened wall of the duodenum. Although this phenomenon can be seen in roentgenograms of previously reported cases, it has not been ascribed to this disease. A correlation appears to exist with the case reported by Malkinson and Rothman,[20] in which a branch of superior mesenteric artery was found to be pressing on the duodenum at postmortem examination.

In the jejunum, there was flocculation of barium and segmentation in 9 patients. Dilated loops of jejunum and ileum were found in 7 patients. Thickening and irregularity of the mucosal pattern of the small bowel were found in 7 patients and delayed transit time was observed in only 5 patients.

Although, some of the small bowel changes are nonspecific (flocculation and segmentation), the others are not found with as great a frequency in any other small bowel disease. We cannot recall seeing the duodenal changes in any other disease. These latter findings are probably specific to scleroderma.

Table II

ROENTGENOLOGIC CHANGES

Type of Abnormality	No. of Cases in Which Occurred
1. Dilatation and retention of barium in the duodenal loop—sometimes for as long as 24 hours	11
2. Flocculation and segmentation of barium in the small bowel	9
3. Dilatation and retention of barium in the duodenal bulb	7
4. Dilatation of loops of small bowel in the jejunum or ileum or both	7
5. Thickening and irregularity of the mucosa in the small bowel	7
6. Delayed transit time	5
7. Dilatation and atony of the stomach	3
8. Partial small bowel obstruction	1

Table III

RELATIONSHIP OF ESOPHAGEAL ABNORMALITIES AND SMALL BOWEL ANORMALITIES

	No. of Cases	Per Cent
Abnormal esophageal studies with normal small bowel studies	11	27.5
Normal esophageal studies with abnormal small bowel studies	2	5.0
Abnormal esophageal studies with abnormal small bowel studies	14	35.0
Normal esophageal studies with normal small bowel studies	13	32.5
	40	100

Since the esophageal changes have been used as a baseline of gastrointestinal involvement in cases of scleroderma and actually are used as a diagnostic aid, we have attempted to relate the small bowel changes to the esophageal changes. Fifty of the 52 patients of whom we had esophageal and small bowel studies showed abnormal esophageal patterns (fluoroscopic or roentgenographic) compatible with scleroderma; the remaining 2 patients had normal esophageal studies. In the second group of 40 patients from this study, we were able to compare the incidence of esophageal abnormalities with that of small bowel changes (Table III). We believe that it is extremely interesting that 2 of the patients (5 per cent) had normal esophageal studies with abnormal small bowel studies.

ROENTGENOLOGIC CHANGES CORRELATED WITH SYMPTOMATOLOGY

We also felt that it would be interesting to relate symptoms to the abnormal roentgenologic changes. For this purpose we were able to take a series of 21 cases, in which we had both esophageal and small bowel studies, and the history was thorough enough for evaluation. In the esophageal symptomatology, we included dysphagia, heartburn, postcibal regurgitation and substernal fullness on swallowing. In the ab-

Table IV

RELATIONSHIP OF SYMPTOMS TO ABNORMAL ROENTGENOLOGIC CHANGES

	Esophageal Symptoms	Abdominal Symptoms	No Gastro-intestinal Symptoms
Abnormal esophageal studies with abnormal small bowel studies	6	5	7
Normal esophageal studies with abnormal small bowel studies	1	2	0
		Total—21 Cases	

dominal symptomatology, we included pain (constant or crampy), epigastric burning, nausea, vomiting, and diarrhea. This series was limited to those patients having either esophageal or abdominal symptoms or no symptoms; patients with symptoms referable to both areas or with vague, poorly defined symptoms were eliminated. Table IV shows the distribution within this group. Seven patients had no gastrointestinal symptoms but had abnormal findings in the esophagus and small bowel, one patients had only esophageal symptoms but had normal esophageal and abnormal small bowel studies, and 6 patients had only esophageal symptoms but had abnormal esophageal and small bowel studies. Thus, a total of 14 patients, 67 per cent of this particular series and 27 per cent of the total series had abnormal roentgenographic small bowel changes in the absence of abdominal symptomatology. Two other patients at Duke Hospital, who were not included in this group and who had abnormal esophageal studies but no small bowel studies, presented no gastrointestinal symptomatology, yet, at postmortem examinations had pathologic involvement of the esophagus and small bowel.

The following cases are examples of the phenomenon we have discussed.

ILLUSTRATIVE CASES

Case 1. (Fig. 1 and 2). The patient, a 32 year old white male, had experienced Raynaud's phenomenon for a period of 1 year, and dysphagia of 1 month's duration. He had no abdominal symptoms. His esophagus was dilated and atonic.

Figure 1 shows barium in the stomach and duodenum. The stomach is slightly enlarged. The duodenal loop is greatly dilated. The sharp line across the transverse duodenum is well demonstrated. There is slight exaggeration of the mucosa in the visualized loops of jejunum. Figure 2 shows the barium retention in the duodenal bulb faintly outlining the pylorus.

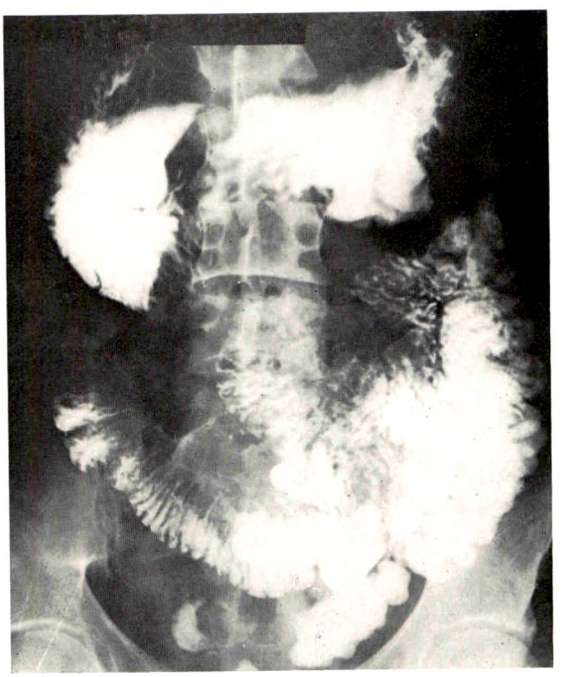


Fig. 1. Case 1. One hour roentgenogram showing dilatation of the duodenal bulb and loop and a sharp smooth shelf in the proximal portion of transverse duodenum.

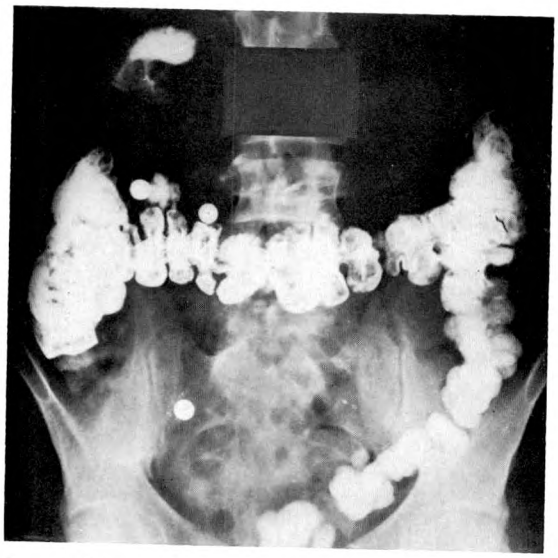


Fig. 2. Case 1. Seven hour roentgenogram showing retention of barium in the duodenal bulb outlining the base of the bulb and the pyloric canal.

Case 2. (Fig. 3). This patient, a 45 year old white female, had experienced Raynaud's phenomenon and intermittent heart burn for a period of 5 years and recurrent lower abdominal pain for 5 months.

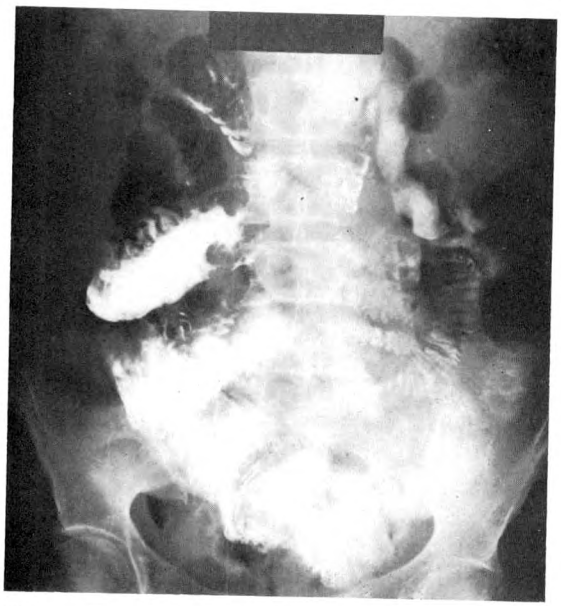


Fig. 3. Case 2. Three hour roentgenogram showing diffuse dilatation of the small bowel with thickening of the mucosal folds. There is an air contrast effect in the duodenal bulb and descending duodenum.

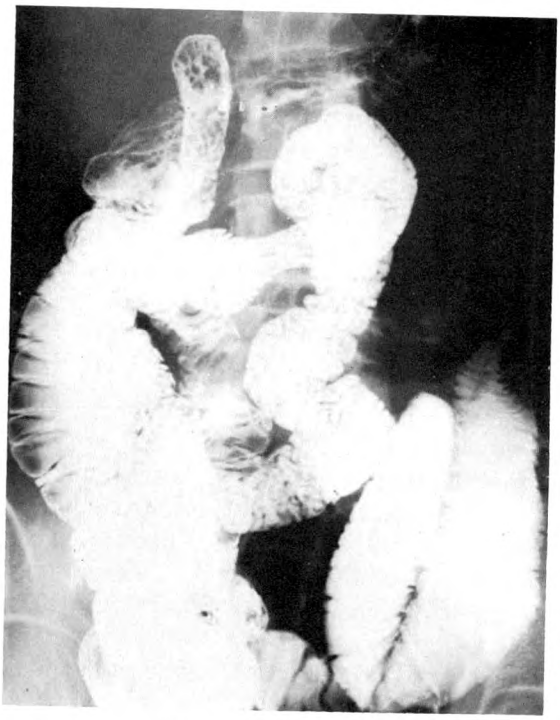


Fig. 4. Case 3. Thirty minute roentgenogram showing diffuse dilatation of the small bowel with minimal but definite thickening of the mucosal folds.

Figure 3 shows the dilated loops of jejunum and ileum with large, somewhat irregular folds; the pattern of diffusely dilated small bowel. Close observation also shows, at 3 hours, the presence of an air contrast pattern in a dilated loop in the right upper quadrant at the level of L2 and L3. This is the descending limb of the duodenum.

Case 3. (Fig. 4). This patient, a 55 year old white female, has previously been reported as a single case of steatorrhea with scleroderma by Horswell *et al.*[15] She had experienced intermittent (twice a year) episodes of crampy, abdominal pain with diarrhea for a period of 20 years. The stool was foul and floated and fat absorption studies were abnormal. In the previous 5 years, the attacks were more frequent and she had lost weight. Roentgenograms showed diffuse dilatation of the entire small bowel. Barium progressed readily through the small bowel and reached the cecum at 4 hours. A subsequent laparotomy showed a short, narrowed segment of distal ileum which was re-

sected and histologically proved to be scleroderma.

Comment. There are several reports in the literature of patients presenting clinical symptoms of intestinal obstruction but who, at laparotomy, showed no narrowed segments. This case is probably the first reported in which a narrowed segment in the small bowel was pathologically diagnostic of scleroderma.

SUMMARY

1. A series of 23 patients with scleroderma of the small bowel and abnormal roentgenologic small bowel patterns has been analyzed for the frequency of various findings previously reported in the literature.

2. The importance of barium retention in the duodenal bulb and loop for as long as 24 hours as a diagnostic aid is stressed.

3. Patients with scleroderma may show abnormal small bowel patterns in the absence of abdominal symptoms.

4. These patients may also show abnormal small bowel patterns in the presence of an apparantly normal esophagus.

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ROENTGEN STUDY OF THE SMALL BOWEL IN ADULTS AND CHILDREN WITH NEOSTIGMINE*

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ROENTGEN examination of the esophagus, stomach, duodenum, and colon has attained a high level of accuracy and efficiency. However, examination of the small intestine has not shared equally in this progress. Although many disease processes can involve the small bowel, clinical suspicion of their presence is often lacking. In particular, it is rare for benign[2] or malignant[5] tumors to be found before the development of complications, such as hemorrhage or obstruction, or at a time when therapy may be curative. Roentgen examination often fortuitously reveals small bowel lesions entirely unsuspected clinically.[4] Therefore, accurate and comprehensive roentgen survey of small bowel in a routine fashion, as is done for the remainder of the gastrointestinal tract, is a necessary adjunct to upper gastrointestinal tract examination.

The two primary deterents to adequate routine roentgen examination of the small bowel in all age groups are the long time required for the passage of barium sulfate suspension through the small bowel (a minimum of 1–4 hours[13]) and the need for multiple roentgenographic exposures to study its entire length. An additional disadvantage in infants and young children is the high incidence of segmentation and flocculation.

Recognizing the need for a practical method of reliably evaluating the small intestine in a reasonable period of time, various investigators have devised procedures to improve either the speed of barium transport or the accuracy of roentgen diagnosis. Small bowel examination may be accomplished by serial roentgenograms following barium meal ingestion or, in part, by refluxing barium through a patent ileocecal valve during barium enema examination of the colon. Proposed methods of accelerating passage of barium through the small bowel have included the use of ice water and/or ice saline[15,18] with the barium, as well as giving large quantities of barium. More accurate evaluation of specific portions of the small bowel may be accomplished by the small bowel enema study[16] or its modifications.[1,6,9]

The numerous techniques described above, however, are all lacking in one or more respects. Some involve varying degrees of patient cooperation and/or discomfort. Some allow superimposition of barium-filled small bowel loops, which limits accuracy by preventing evaluation of each individual loop. Finally, some may be indicated only after the development of complications of small bowel pathology and, therefore, do not lend themselves to routine use in the early diagnosis of small bowel lesions.

Neostigmine methylsulfate is a reversible inhibitor of acetylcholinesterase and protects acetylcholine from enzymatic hydrolysis, permitting it to act in a prolonged and intensified manner.[8] The administration of neostigmine, therefore, produces a sustained action of acetylcholine in the body, the effect of which on the bowel is an increase in amplitude and frequency of propulsive activity and, hence, intestinal motor transport.[8,10] This effect of acetylcholinesterase inhibitors has been used to decrease intestinal gas prior to abdominal roentgenology[3] and in the treatment and prophylaxis of postoperative paralytic ileus.[7,10,12,17] Ingelfinger and Moss[11] have shown neostigmine to be ineffective in

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changing the bowel motility in sprue. The rationale and precedent for the use of neostigmine in gastrointestinal roentgenology thus established, Margulis and Mandelstam[14] previously have evaluated its efficacy in barium meal examination of the small bowel. We have undertaken to compare its use with that of ice cold saline and ice water in improving roentgen examination of the small bowel. In addition, we have studied the efficacy of neostigmine in evaluation of the small bowel of infants and children.

PROCEDURE

One group of 239 adults was given 200 cc. of USP barium sulfate mixed with 400 cc. of ice cold saline. A second group of 240 adults was given 200 cc. of USP barium sulfate mixed with 400 cc. of water at room temperature. Routine study of the esophagus, stomach, and duodenum was performed in all patients by means of fluoroscopic examination, spot roentgenograms, and conventional roentgenograms. Neostigmine methylsulfate (Prostigmine-Roche) was then injected subcutaneously in all patients in the second group. Adults who weighed less than 190 pounds were given 0.50 mg., and those who weighed more than 190 pounds were given 0.75 mg. Roentgenograms of the abdomen were then made at 15 minutes, 60 minutes, and at one hour intervals, as necessary, until the barium had entered the cecum. Each patient was evaluated with respect to both the speed of small intestinal transport and the quality of small bowel pattern. An optimum pattern was considered to be one in which all small bowel loops were filled with barium and could be individually visualized in continuity. The patients were randomized and identified by number so that the observer did not know the group to which any given patient belonged. In a similar study the effect of a mixture of barium with ice water was evaluated in a group of 57 patients.

One hundred and thirty examinations on 127 patients in the pediatric age group were performed. Examination of the small bowel of infants and children differed only slightly from that of the adults. Micropaque was used rather than USP barium sulfate, because with its use the small bowel pattern of children in the 2 to 8 year age group more closely approximated that of the adult. Depending on the size of the patient, approximately 100–200 ml. of barium-water mixture was used. No additional food or barium was administered during the course of the examination. Between roentgenograms infants were placed in the right lateral decubitus position, while older children walked about. Following completion of fluoroscopy, spot roentgenography and conventional roentgenography of the esophagus, stomach, and duodenum, neostigmine was injected subcutaneously. After utilizing a number of dosage schedules, it was found that infants and children required a relatively large amount of neostigmine. For the patients reported in this paper 0.25 mg. was used in infants under 2 years of age, and 0.50 mg. was used for those over that age. Roentgenograms were taken every 15 minutes until the barium reached the cecum. Since it often is difficult to distinguish the ileum from the colon in infants, additional roentgenograms supplemented at times with fluoroscopic spot roentgenograms were obtained for confirmation of the impression that the barium had reached the cecum.

RESULTS

The results of the comparative study of the usefulness of neostigmine and ice saline in improving the speed of small bowel transport and the quality of small bowel examination in adults are listed in Table I and II, respectively. It will be noted (Table I) that the time required for the barium to reach the cecum is essentially the same whether neostigmine or ice saline be used, *i.e.*, in approximately 72 per cent of patients the barium will have reached the cecum within 60 minutes. However, the use of neostigmine provided some improvement in the quality of the small bowel examination, as

Table I

TIMES OF APPEARANCE OF BARIUM IN THE CECUM

	15 min.	60 min.	120 min.	>120 min.	
Neostigmine	59 (25%)	116 (47%)	50 (21%)	15 (6%)	240 patients
Iced Saline	62 (26%)	110 (46%)	48 (20%)	19 (8%)	239 patients
Iced Water	9 (15%)	22 (38%)	19 (33%)	8 (14%)	57 patients

Table II

DIAGNOSTIC QUALITY OF SMALL INTESTINAL PATTERN

	Excellent	Good	Poor	
Neostigmine	71 (30%)	99 (41%)	70 (29%)	240 patients
Iced Saline	50 (21%)	102 (43%)	87 (36%)	239 patients
Iced Water	11 (19%)	17 (30%)	29 (51%)	57 patients

indicated in Table II. Here it will be noted that 71 per cent of patients receiving neostigmine demonstrated an excellent or good small bowel pattern, whereas 64 per cent of those receiving ice saline did so. The results of this study are further shown in Table III, which combines the findings with respect to both time of barium transport and quality of small intestinal pattern. The use of a barium-ice water mixture was obviously inferior to either neostigmine or ice saline in the relatively small group studied.

In the pediatric age group, the times required for the barium to reach the colon are listed in Table IV. The barium was in the colon at the time of the 15 minute

Table III

QUALITY OF SMALL BOWEL EXAMINATION AMONG PATIENTS STUDIED WITH TRANSIT TIMES OF 60 MINUTES OR LESS

(72% of patients in both neostigmine and iced saline groups)

	Excellent	Good	Poor	
Neostigmine	69 (39%)	67 (38%)	39 (22%)	175 patients
Iced Saline	45 (26%)	74 (43%)	53 (31%)	172 patients

Table IV

TRANSIT TIME IN INFANTS AND CHILDREN GIVEN NEOSTIGMINE

Age	No. of Examinations	Barium in Colon in Roentgenograms Taken at:			
		15 min.	30 min.	45 min.	1 hr. or more
0–3 mo.	25	10	12	—	3
4–12 mo.	15	2	11	1	1
13–24 mo.	15	2	5	5	3
2–4 yr.	15	5	5	4	1
5–8 yr.	25	10	12	2	1
9–14 yr.	35	8	18	3	6
Totals	130	37 (28.5%)	63 (48.5%)	15 (11.5%)	15 (11.5%)

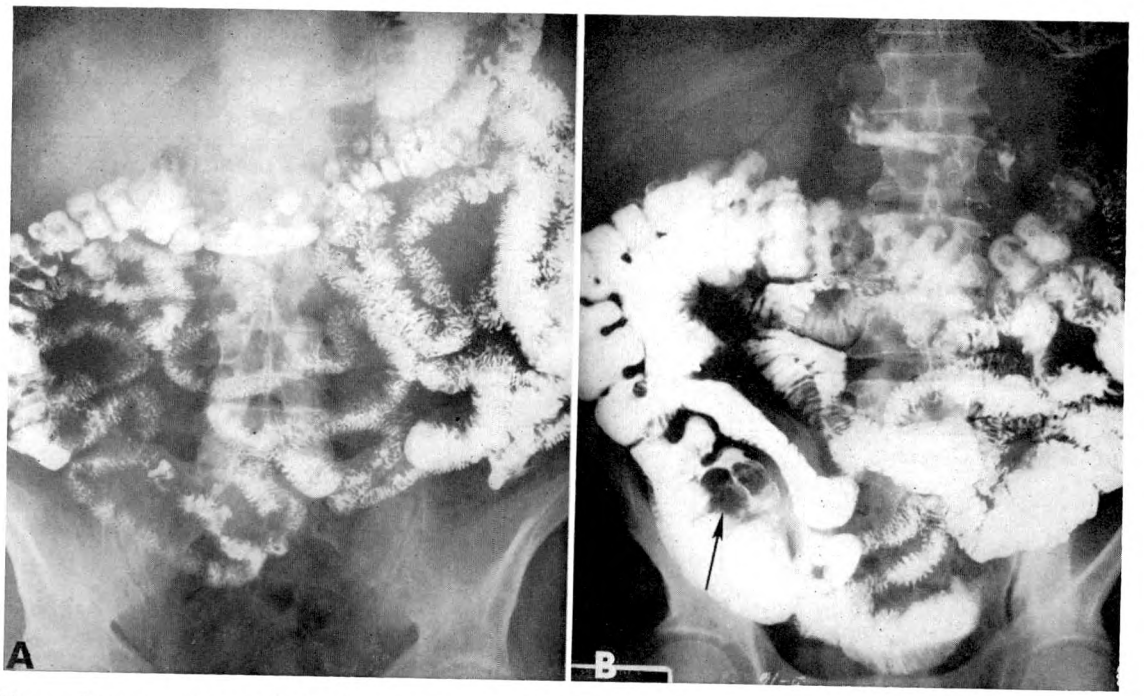


FIG. 1. In most patients the barium meal reaches the colon within one hour after the injection of neostigmine. The entire small bowel can thus be evaluated. Lesions in the proximal colon can often be discovered. (*A*) Prone roentgenogram of the abdomen 15 minutes after the injection of neostigmine. The entire small bowel and proximal colon are visualized in continuity and are normal. (*B*) One hour roentgenogram demonstrating a normal small bowel. However, there is a polypoid mass (arrow) in the region of the ileocecal valve which proved to be metastatic tumor from a silent renal cell carcinoma.

roentgenogram in 28.5 per cent, within 30 minutes in an additional 48.5 per cent, and at 45 minutes in an additional 11.5 per cent. Therefore, 77 per cent of all pediatric patients had transit times of 30 minutes or less and 88.5 per cent had transit times of 45 minutes or less. Six of the 15 cases with transit times of one hour or more were cases of either malabsorption syndromes or malrotation.

The presence of gastric retention did not seem to correspondingly increase the transit time in infants and children, as long as some barium left the duodenum. The high incidence of segmentation and flocculation of barium in the small bowel of infants and young children was decreased with the use of finely pulverized barium (micropaque) and was further reduced with the use of neostigmine. This was particularly evident in the group between 2 and 8 years of age and is believed to be related to the faster transit time. However, except for this decreased segmentation and flocculation, the poor mucosal fold detail present in infants, especially in the first few months of life, was not appreciably altered by neostigmine or micropaque. In children 9 or more years of age, the use of micropaque alone was found sufficient to produce a small bowel pattern essentially adult in character.

DISCUSSION

Neostigmine produces an increased motility of the barium meal, as well as an increased tonus of the individual small bowel loops as demonstrated roentgenographically, usually producing uninterrupted filling of the entire small intestine from duodenum to colon within one hour of its injection (Fig. 1*A*). We have found that use of neostigmine allows a reliable evaluation of the small bowel with respect to all disease processes which may be en-

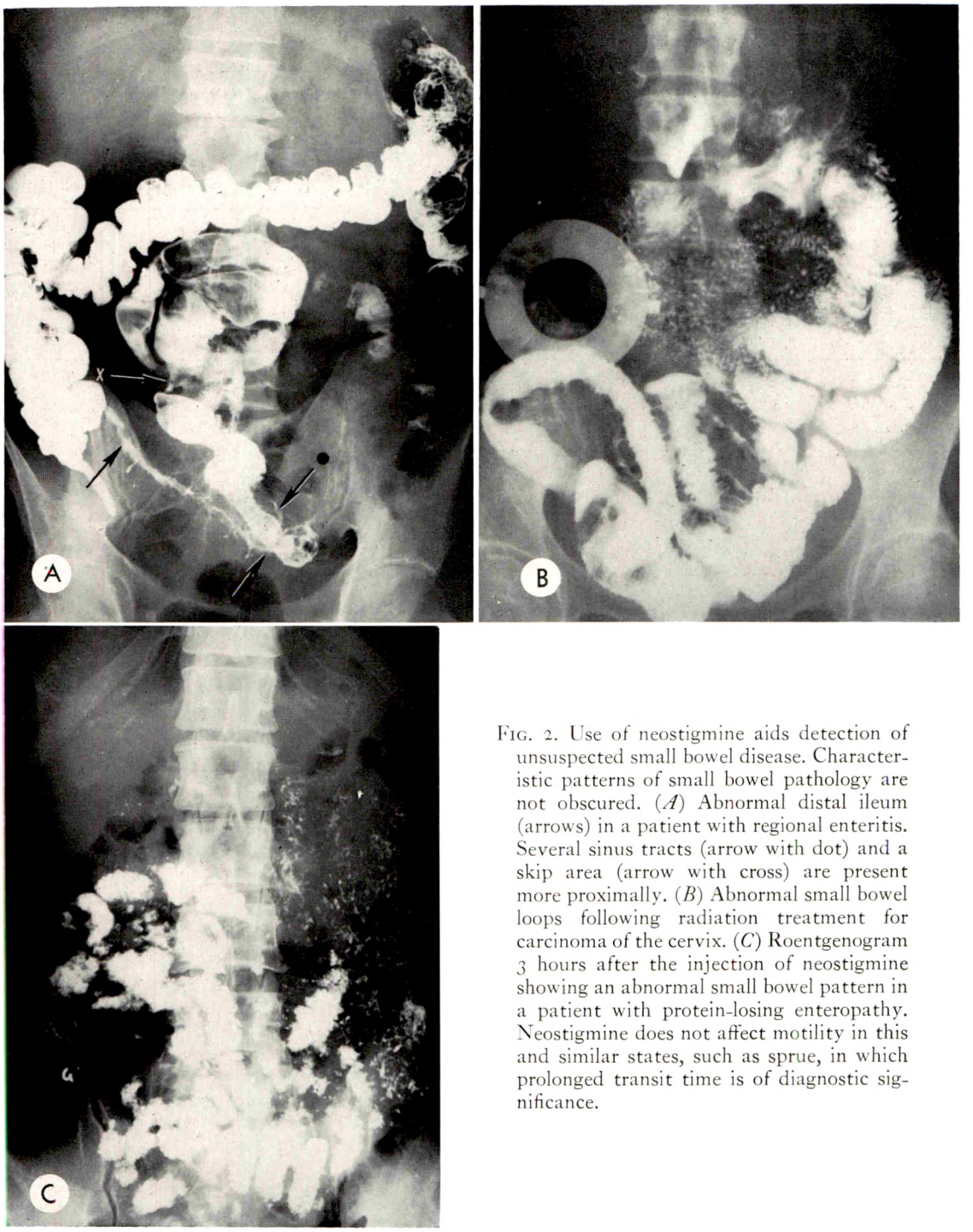


Fig. 2. Use of neostigmine aids detection of unsuspected small bowel disease. Characteristic patterns of small bowel pathology are not obscured. (*A*) Abnormal distal ileum (arrows) in a patient with regional enteritis. Several sinus tracts (arrow with dot) and a skip area (arrow with cross) are present more proximally. (*B*) Abnormal small bowel loops following radiation treatment for carcinoma of the cervix. (*C*) Roentgenogram 3 hours after the injection of neostigmine showing an abnormal small bowel pattern in a patient with protein-losing enteropathy. Neostigmine does not affect motility in this and similar states, such as sprue, in which prolonged transit time is of diagnostic significance.

countered there (Fig. 2, *A*, *B* and *C*). Since the contracted bowel loops can be easily followed, localized abnormal areas can be more readily identified (Figs. 1*B* and 3, *A*, *B* and *C*). Generalized bowel disease strikingly changes the normal pattern (Fig. 4*B*). Neostigmine, furthermore, significantly decreases the segmentation and flocculation in

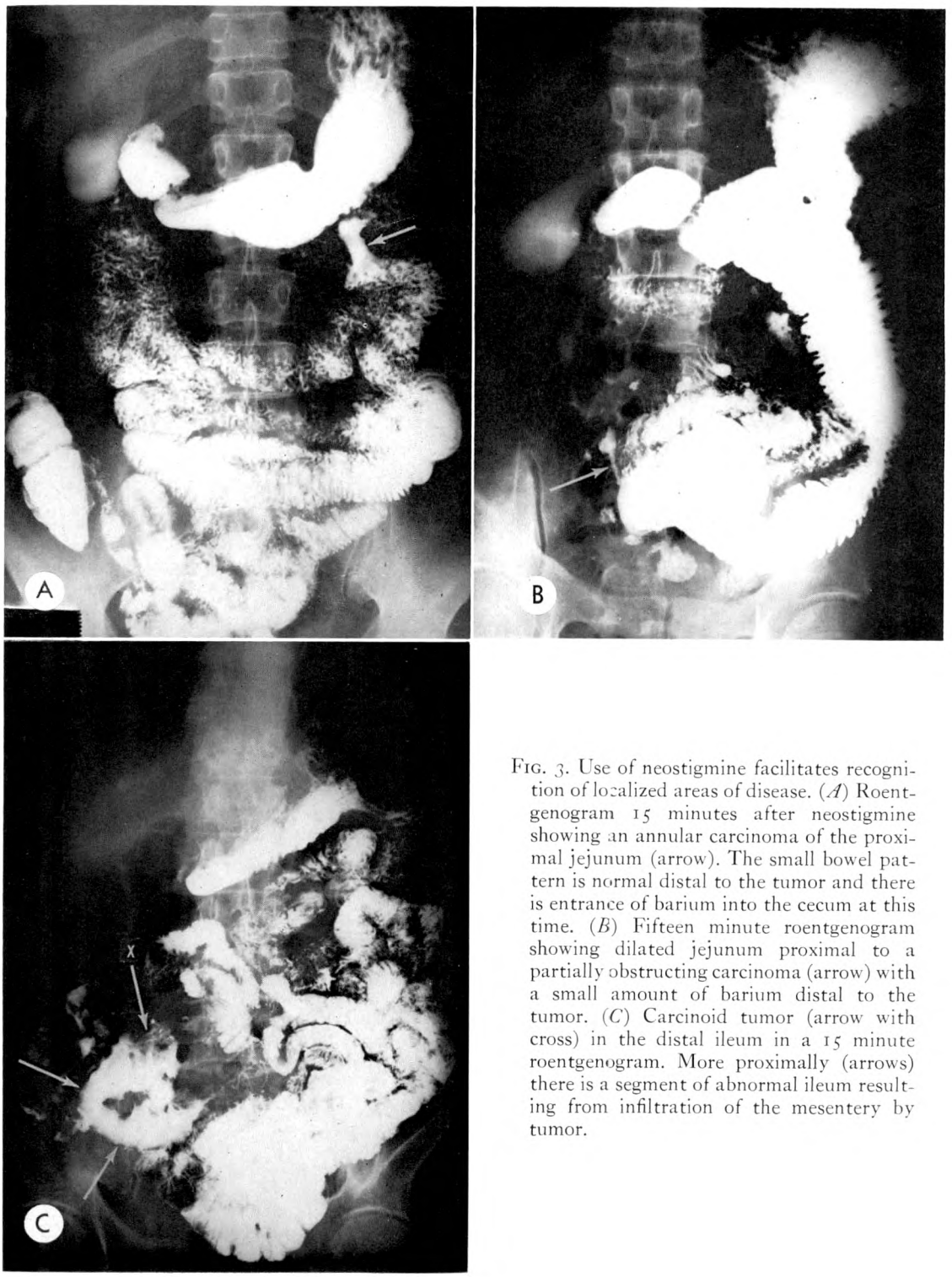


FIG. 3. Use of neostigmine facilitates recognition of localized areas of disease. (*A*) Roentgenogram 15 minutes after neostigmine showing an annular carcinoma of the proximal jejunum (arrow). The small bowel pattern is normal distal to the tumor and there is entrance of barium into the cecum at this time. (*B*) Fifteen minute roentgenogram showing dilated jejunum proximal to a partially obstructing carcinoma (arrow) with a small amount of barium distal to the tumor. (*C*) Carcinoid tumor (arrow with cross) in the distal ileum in a 15 minute roentgenogram. More proximally (arrows) there is a segment of abnormal ileum resulting from infiltration of the mesentery by tumor.

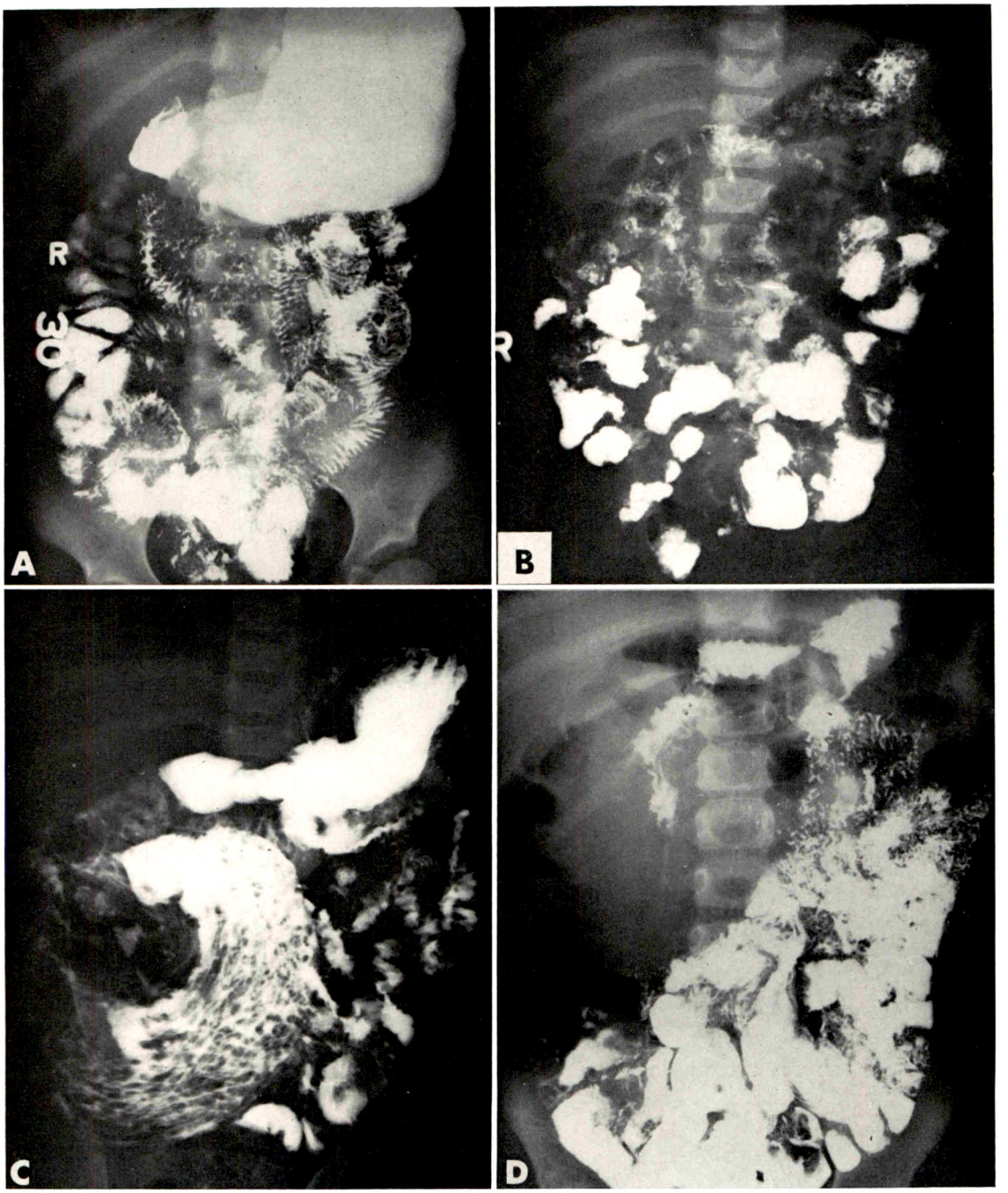


Fig. 4. Neostigmine is valuable in studying the small bowel in the pediatric age group. (*A*) Normal small bowel in a roentgenogram taken 30 minutes after injection of neostigmine in a one year old patient. There is decreased segmentation and flocculation and the small bowel pattern closely approximates that of an adult. (*B*) Forty-five minute roentgenogram of a one year old child with celiac disease showing the abnormal small bowel pattern. (*C*) Roentgenographic demonstration of ascariasis within the small bowel of a patient with a large, palpable abdominal tumor. (*D*) Thirty minute roentgenogram of a 5 year old boy with a large omental cyst in the right upper quadrant. The duodenum and ureter are not displaced. The small bowel which maintains its normal pattern is displaced.

normal infants and young children (Fig. 4*A*). The accelerated transit time associated with neostigmine was of particular value in the rapid evaluation of malrotation and abdominal masses in the pediatric age group (Figs. 4, *C* and *D*). In the former condition the position and mobility of the cecum are often more important roentgenographically in the diagnosis than is the location of the duodenum and proximal small bowel.

Fluoroscopy and spot roentgenography of areas of interest as noted on conventional roentgenograms are not precluded by this technique. Gastric emptying stimulated by neostigmine makes re-examination of suspicious areas of the stomach or duodenum quite feasible during the same upper gastrointestinal tract examination, obviating recourse to repeat study another day. The injection of neostigmine is simple and painless. Its cost is less than that of a single roentgenogram. The technique lends itself quite readily to use in both small and large volume practice as an integral part of routine roentgen examination of the upper gastrointestinal tract.

Based on our findings in the studies described above, all patients having upper gastrointestinal tract examination in our department are routinely given neostigmine in the dosage described. In adults, we now routinely obtain roentgenograms of the abdomen 15 minutes and, if necessary, at hourly intervals after injection of neostigmine. Rarely is it necessary to obtain a roentgenogram later than one hour after injection. In the pediatric age group, following injection of neostigmine, roentgenograms of the abdomen are routinely obtained every 15 minutes for one hour and as judged necessary thereafter until the barium has entered the cecum.

Neostigmine has now been used routinely in over 10,000 upper gastrointestinal tract examinations with essentially no untoward results. A few patients complained of cramping. One patient developed perspiration, vomiting, and brachycardia which were promptly relieved by the injection of 1/150 gr. of atropine. The only patients not given neostigmine are those in whom there are clinical contraindications to its use, such as intussusception, volvulus, complete intestinal obstruction, perforation, or peritonitis.[8,17] The one additional precaution practiced is refraining from use of neostigmine in patients with a history of recent myocardial infarction. It is important to recognize that an intact neuromuscular system of intestinal innervation is a prerequisite for adequate responses of the bowel to neostigmine. Our observations confirm those of others[11,14] that motility will not be increased in advanced sprue and neuromuscular disorders of the small intestine. Also, patients receiving antispasmotic medication or patients who are severely nauseated have demonstrated decreased motility and transit time.

SUMMARY

The subcutaneous injection of neostigmine methylsulfate in the dosages described has been successfully used in over 10,000 roentgen examinations of the upper gastrointestinal tract. It has provided by its action of increasing small bowel tonus and motility a safe, accurate, and reliable method of routinely studying the entire small intestine in adults and children.

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METASTATIC TUMOR OF THE SMALL INTESTINE*

THREE CASES PRESENTING UNUSUAL CLINICAL AND ROENTGENOGRAPHIC FINDINGS

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ALTHOUGH diseases of the small intestine including primary tumors are extensively described in the literature,[4–8, 10–12,15–17] the authors have found little information about metastatic lesions of the small bowel,[1–3,7–9,13,14] particularly in patients who are not known to have a primary malignancy and who seek medical attention because of abdominal symptoms suggesting severe disease of the small intestine. Three patients with unsuspected extensive metastatic lesions of the small bowel have recently been studied at The New York Hospital. These patients presented confusing and unusual clinical and roentgenographic findings.

REPORT OF CASES

Case I. (Fig. 1, *A* and *B*). This 62 year old white male was admitted to The New York Hospital because of hemoptysis. He had been a heavy cigarette smoker. He denied weight loss, fever or gastrointestinal complaints. The physical examination was unremarkable.

A chest roentgenogram (Fig. 1*A*) showed a round soft tissue mass in the left lower lobe compatible with a bronchogenic carcinoma.

At thoracotomy there was a tumor mass at the junction of the left upper and lower lobes. A left pneumonectomy was done and the pathologic diagnosis was carcinoma of the lung. Hilar lymph nodes were free of tumor. He did well postoperatively and was discharged.

The patient was readmitted 5 months later with a 2 week history of a constant right abdominal dull ache associated with 4 to 6 daily soft to liquid bowel movements. On physical examination there was abdominal guarding and a 15 cm. tender mass in the right lower quadrant of the abdomen.

Laboratory examination showed a hemoglobin of 8.6 gm. per cent and a normal white blood cell count. Four stools were guaiac negative. Roentgenographic studies of the colon, esophagus and stomach were normal. A small bowel series (Fig. 1*B*) revealed matting together of loops of ileum and marked dilatation of at least two ileal segments suggesting obstruction. There appeared to be extraluminal barium in an abscess cavity. The clinical and roentgenographic impression was regional enteritis with an abscess.

At laparotomy there was a mass in the mesentery of the ileum which caused partial small bowel obstruction. The involved mesentery and small bowel were resected. Gross examination of the specimen revealed a 12 cm. tumor mass in the mesentery of the ileum. The tumor had a large necrotic center which freely communicated with two loops of ileum. Morphologically, it was similar to the one which had previously been removed from the left lung. The patient died 3 months later.

Case II. (Fig. 2, *A* and *B*). This was a 49 year old white female admitted to The New York Hospital because of dysphagia and diarrhea. Four years previously she had a right radical mastectomy for carcinoma of the breast.

Eight months prior to the present admission, she began to have abdominal cramps and diarrhea about 3 hours after each meal. She also noted progressive dysphagia at first with solid foods and later with liquids. She had lost 58 pounds.

Besides signs of obvious weight loss and a right radical mastectomy, positive physical findings were limited to the abdomen. There was a 5×7 cm. firm, smooth, easily movable, tender mass in the right lower quadrant of the abdomen.

Complete blood count and urinalysis were normal. A stool guaiac test was negative. A chest roentgenogram was normal. Esophagoscopy revealed a cobblestone appearance of the esophageal mucosa at 33 cm. and biopsy showed only chronic esophagitis. An esophagram showed some spasm of the distal esophagus with intact

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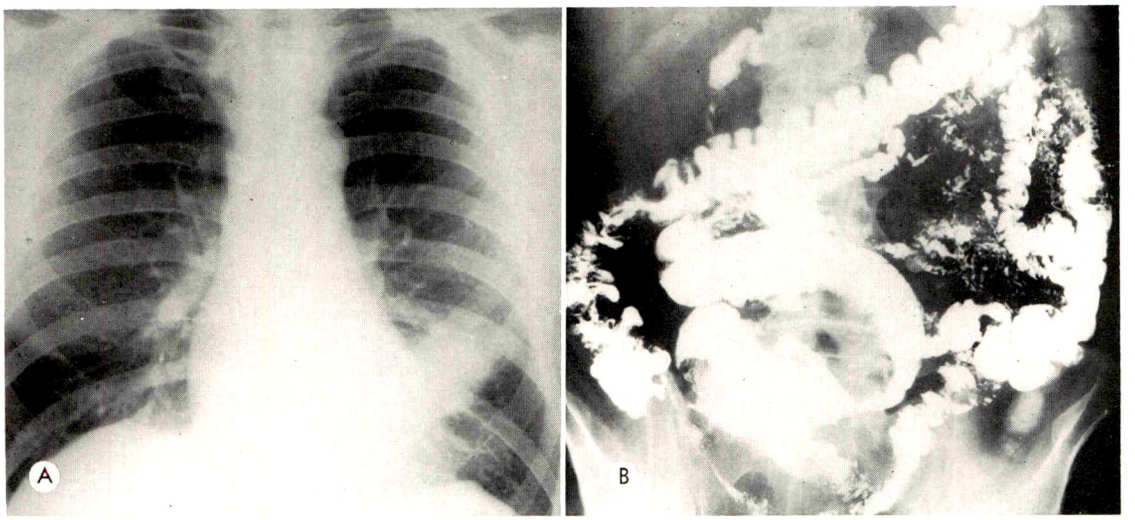


Fig. 1. Case 1. *Bronchogenic carcinoma in a 62 year old male with subsequent metastatic involvement of the terminal ileum.* (*A*) Frontal teleroentgenogram of the chest showing a 4 cm. peripheral bronchogenic carcinoma in the left lower lung field. (*B*) A conventional study of the small bowel (1 hour delay) showing areas of dilatation, constriction and extensive destruction of several loops of ileum. There is a collection of extraluminal barium within a necrotic tumor mass involving the mesentery and ileum. The terminal ileum appeared normal on subsequent roentgenograms.

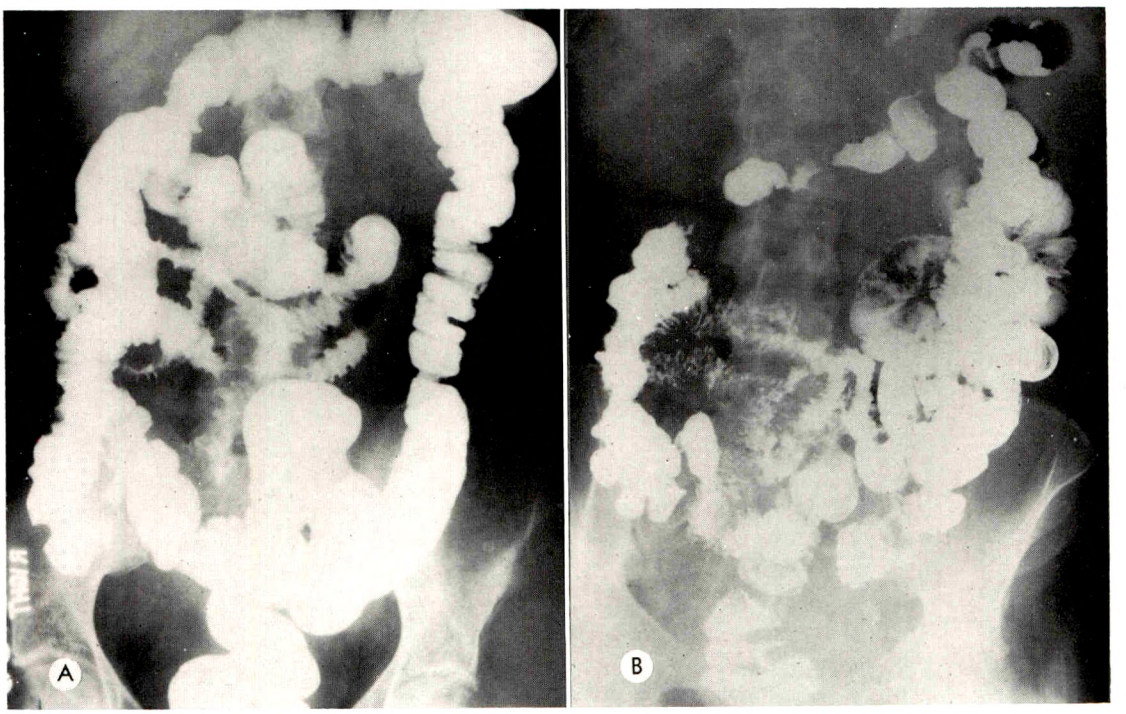


Fig. 2. Case 11. *Metastatic involvement of almost the entire gastrointestinal tract in a 49 year old woman who 4 years previously had a right radical mastectomy for carcinoma.* (*A*) A barium enema study with ileal reflux showing rigidity and irregularity of the walls of the right colon. The visualized ileum shows blunting and thickening of the valvulae conniventes. The loops of ileum do not fill out well and are abnormally separated. (*B*) A 4 hour small bowel study showing similar changes in the ileum and right colon. There are several hair-like projections of barium from the wall of the right colon suggesting ulceration.

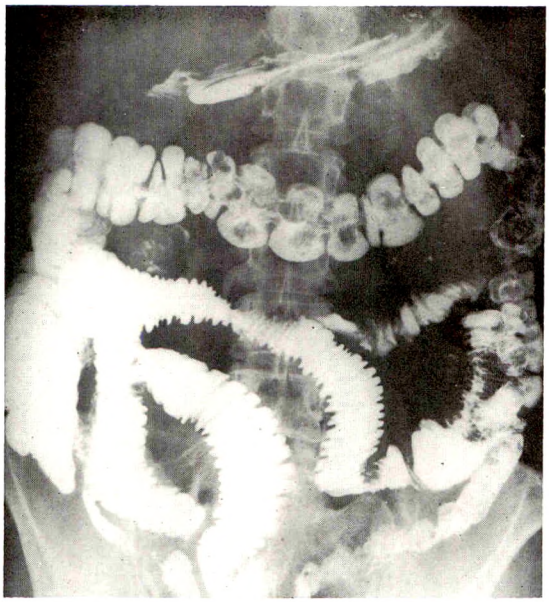


Fig. 3. Case III. *Metastatic involvement of the ileum in a 50 year old woman with primary carcinoma of the sigmoid colon.* An 8 hour delayed small bowel study showing narrowing of the terminal ileum. Proximal loops of ileum are abnormally separated and irregularly dilated.

mucosa. The stomach and duodenum were unremarkable. A barium enema with ileal reflux (Fig. 2*A*) and a small bowel series (Fig. 2*B*) revealed diffuse disease of the terminal ileum and right colon up to the hepatic flexure. There was rigidity, narrowing, shaggy borders and some exaggeration of the mucosal markings in both the colon and ileum. A diagnosis of ileocolitis or lymphoma was made. In addition, there appeared to be unrelated obstruction or spasm of the esophagogastric junction.

At laparotomy there was abdominal carcinomatosis. The serosal surfaces of the stomach, small intestine and right colon were covered with metastatic nodules. The esophagogastric junction and terminal ileum were fixed and extensively involved with metastatic tumor. A biopsy confirmed the diagnosis of metastatic tumor similar in morphology to the primary breast lesion. Following surgery she gradually deteriorated and died 25 days after operation. Autopsy was refused.

Case III. (Fig. 3). This 56 year old white female was admitted to The New York Hospital because of crampy abdominal pain, anorexia, nausea and vomiting, fever, a 12 pound weight loss and diarrhea of 3 weeks' duration. Positive physical findings were limited to the abdomen where there was moderate periumbilical tenderness on deep palpation and an ill defined mass in the right lower quadrant. The complete blood count and urinalysis were normal. Four stool guaiac tests were negative. Proctoscopy to 12 cm. was normal. A chest roentgenogram was normal. A barium enema study and a small bowel series (Fig. 3) showed narrowing of the last 10 cm. of terminal ileum. The ileum proximal to the narrowed segment was mildly dilated with abnormal separation of multiple loops of small bowel. Regional enteritis was thought to be the best diagnostic possibility.

Because of progressive mechanical small bowel obstruction, a laparotomy was done. There were 2 areas of dense adhesions about the ileocecal valve and terminal ileum. The terminal ileum was resected and the ileal wall was found to be markedly thickened, producing almost complete occlusion of the lumen. The mucosa appeared intact. Microscopic examination revealed mucus-producing adenocarcinoma in the wall of the terminal ileum thought to be metastatic. Postoperatively, the patient did well for one month but then was readmitted because of sigmoid obstruction. A second laparotomy revealed a primary obstructing adenocarcinoma of the sigmoid colon identical to that found earlier in the ileum.

CLINICAL DISCUSSION

These 3 patients presented similar problems in diagnosis. In Case I and Case II the past history of primary neoplasm was known; yet the clinical findings on subsequent admission suggested inflammatory disease or lymphosarcoma of the small bowel. Abdominal exploration was performed in Case I because of suspected abscess and in Case II because of intractable dysphagia and a mass in the right lower quadrant of the abdomen. In Case III there was no previous history of malignancy and the finding of extensive metastatic disease at laparotomy was also unexpected. The primary lesion in Case III (sigmoid colon) was not found until one month after the initial laparotomy. The clinical picture of fever, colicky abdominal pain, diarrhea, and a right lower quadrant mass and the roentgenographic picture of diffuse small

bowel disease was present in each case. The usual differential diagnosis considered was regional ileitis or malignant lymphoma. Hypoplastic ileocecal tuberculosis, actinomycosis, sprue and endometriosis seemed less likely from the roentgenographic picture. Also, the extent of the disease seemed to rule out primary small bowel tumor, although malignant carcinoid may present in this fashion.

The clinical evaluation and differential diagnosis of small bowel disease have been clearly defined in the literature, but no mention is made of metastatic tumors presenting the clinical picture seen in these patients. An important differential clinical point in these 3 cases of metastatic disease was guaiac negative stools suggesting lack of mucosal destruction and ulceration. However, mention is made in the literature that metastatic melanoma to the small bowel frequently is associated with gastrointestinal bleeding.[3,14] Rectal bleeding is much more likely to occur in regional enteritis or lymphosarcoma.

Raiford[13] reviewed 50 cases of metastatic tumor to the small bowel. Most of the primary tumors were infradiaphragmatic. Only 5 cases were supradiaphragmatic. In addition most cases had multiple involvement of the small bowel and only 15 cases had isolated involvement of the ileum. It is of interest that 2 of our primary tumors were supradiaphragmatic. We propose that metastatic tumor to the small bowel should be added to the list of diagnostic possibilities of patients presenting the clinical picture described, particularly if the past history of neoplastic disease is positive.

ROENTGENOGRAPHIC DISCUSSION

The serial barium examination of the intestine is of great importance in the detection and proper evaluation of primary and secondary disease of the gastrointestinal tract. However, there are many pitfalls since the changes in a specific disease may be very subtle or so extensive and destructive that one cannot sift out the usual diagnostic points in favor of a particular lesion. The purpose of this paper is to add another differential possibility, metastatic tumor, which may be so extensive and protean in its roentgen manifestations that it is easily confused with chronic inflammatory disease or lymphosarcoma. In Cases I and II the most likely diagnostic possibility was lymphosarcoma, each case having various combinations of the findings of abscess formation, spreading of loops of small intestine, segmental constriction and proximal dilatation, pressure defects and intraluminal filling defects. Case III had constriction of the terminal ileum suggesting regional ileitis. It does not seem possible roentgenographically to make a specific diagnosis of metastatic tumor of the small bowel, but this should be a differential consideration in diffuse small bowel disease. Lack of mucosal destruction would seem to favor metastatic disease over regional enteritis or lymphoma since metastases chiefly involve the serosal and muscular layers of the small bowel wall.[1,9]

SUMMARY AND CONCLUSION

Three patients are presented who had clinical and roentgenographic findings suggesting inflammation or lymphoma of the small bowel. At surgery they were found to have metastatic disease from the lung, breast, and sigmoid colon. The possibility of diffuse metastatic involvement should be considered in the differential diagnosis of small bowel disease, particularly in patients with a past history of a malignancy regardless of its origin or the lapse of time between initial surgery and subsequent gastrointestinal complaints and roentgenographic changes. Intact intestinal mucosa and guaiac negative stools are important differential points favoring metastatic disease.

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ROENTGEN DIAGNOSIS OF APPENDICO-COLIC FISTULATION*

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IN SPITE of efforts to facilitate the early diagnosis and surgical treatment of acute appendicitis, abscess formation continues to be a common complication. In most cases of appendiceal abscess the clinical diagnosis is evident and roentgenologic investigation is not considered helpful or necessary; however, occasionally, when the diagnosis is in doubt, roentgenologic study is requested. Usually such investigation is limited to plain roentgenograms of the abdomen, but, at times, contrast studies of the small or large bowel are performed. Under such circumstances the radiologist most frequently encounters extrinsic pressure deformities of the cecum or terminal ileum on barium enema examination, presumptive corroboration of appendiceal abscess formation.[1] In rare circumstances the actual appendiceal abscess becomes opacified through filling via fistulae connecting the appendiceal abscess to the large bowel. Reports of fistulae of this nature are sparse in the American medical literature. Dale described a single case of appendiceal-sigmoid fistulation.[2] River and Gradinger reported an appendico-colic fistula examined roentgenologically but not diagnosed preoperatively.[3] In this latter case, fistulation had occurred between the appendiceal abscess and ascending colon.

In the 2 cases to be reported, appendico-colic fistulation was diagnosed by barium enema study preoperatively. In one case fistulation occurred between the appendiceal abscess and the sigmoid colon, and in the other, between the abscess and the ascending colon.

REPORT OF CASES

CASE 1. R. M., a 53 year old male, was admitted on April 27, 1959 with a history of abdominal pain of 12 hours' duration. The pain had begun in the epigastrium and had become generalized throughout the abdomen. There was nausea but no vomiting. The abdomen was distended and rigid and there was generalized rebound tenderness. Peristalsis was diminished. The white blood cell count was 7,500 with 85 per cent neutrophils. The temperature was 102.6°F., pulse 100, and respiration 20. Plain roentgenograms of the abdomen suggested a paralytic ileus without localizing signs. There was no evidence of free air in the peritoneal cavity. The provisional clinical diagnosis was that of peritonitis due to perforated appendix or peptic ulcer. Treatment was conservative with gastric suction, parenteral feeding, and antibiotics with gradual improvement. A subsequent cholecystographic study was negative as was an upper gastrointestinal series. On May 12, 1959, the initial barium enema examination was performed. At fluoroscopy an extraluminal barium collection appeared during the filling of the sigmoid colon. This barium collection (Fig. 1) measured about 6 cm. in diameter. Its origin from the sigmoid colon appeared obvious (Fig. 2). Several diverticula were demonstrated at a higher level in the postevacuation study (not illustrated). The presumption was, therefore, that the extraluminal barium collection represented an abscess secondary to a perforated colonic diverticulum. Although the vermiform appendix was opacified, its abnormality was not appreciated at the time of the initial barium enema study. Retrospectively, however, it was noted that it was directed medially, appeared straightened, and that its lumen was narrowed, particularly at the base where there was an associated concave defect of the cecum. The tip approximated the extravasated barium collection communicating with the sigmoid (Fig. 3).

The patient was continued on conservative management and discharged on May 20, 1959. A follow-up contrast examination of the colon 6 weeks later demonstrated a satisfactory alteration. The extraluminal collection and fistula arising from the sigmoid colon were no longer visualized. At the site of this former disease

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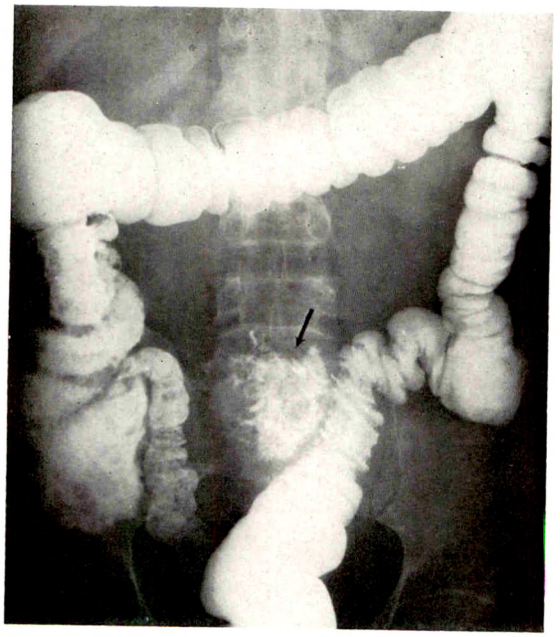


FIG. 1. Case 1. Initial barium enema examination showing extraluminal extravasation (appendiceal abscess) medial to sigmoid.

process, there was noted only a localized shallow indentation of the medial wall of the colon. On this occasion, the vermiform appendix was again opacified and not partially obscured by ileal filling so that its abnormal position and configuration were more obvious. A localized area of attenuation suggesting intramural edema was observed at the appendiceal base (Fig. 4). It was believed, therefore, that initially the extraluminal collection adjacent to the sigmoid actually represented an appendiceal abscess which had ruptured into the descending

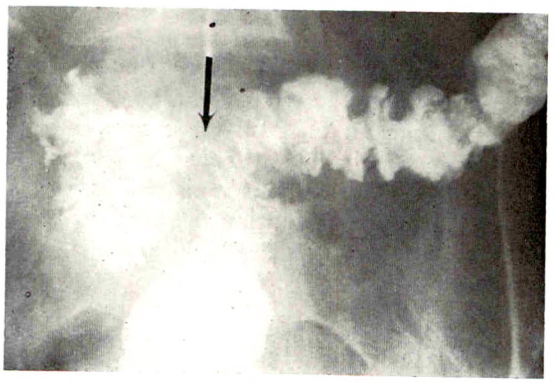


FIG. 2. Case 1. Spot roentgenogram of sigmoidal region demonstrating fistula between appendiceal abscess and sigmoid.

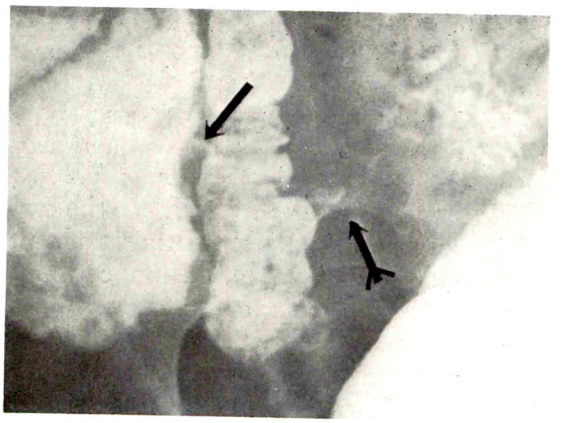


FIG. 3. Case 1. Magnified view of cecal-appendiceal area. Left arrow points to luminal narrowing of base of vermiform appendix (partially obscured by terminal ileum) and concave deformity of cecum. Right arrow points to tip of appendix adjacent to appendiceal abscess.

colon creating an appendico-colic fistula. In the interval between the two investigations, the abscess had apparently drained into the sigmoid colon with spontaneous healing of both it and the fistula, although continued roentgen evidence of appendiceal inflammation appeared to persist. Clinically, however, the patient improved and was discharged in June, 1959.

The patient was readmitted on September 2, 1959 because of recurrent abdominal pain. Exploratory laparotomy performed 6 days later revealed the vermiform appendix to be distended in its mid-portion and to be bound down retrocecally to the root of the mesentery. A retrograde appendectomy was performed. No evidence of abscess formation was noted in the abdomen. The final pathologic diagnosis was acute suppurative appendicitis. The patient made an uneventful recovery and was discharged on September 28, 1959.

CASE II. A. N., a 65 year old male, was transferred from another hospital with a provisional diagnosis of neoplasm of the cecum on August 22, 1961. Five weeks before admission this patient had experienced acute colicky right lower quadrant pain which reached its maximum severity after 2 days. Suddenly, there was complete relief from the pain for one day and since that time only intermittent and relatively mild pain had been present. Constipation accompanied the onset of the pain, and persisted for 3

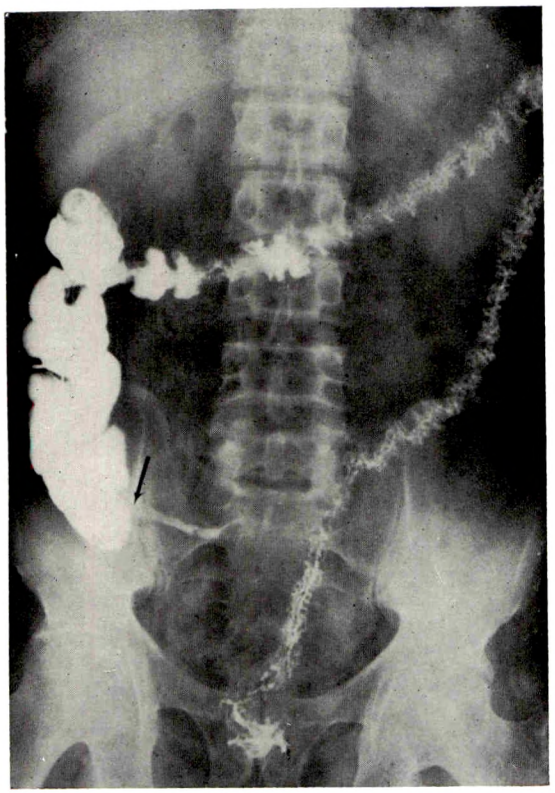


Fig. 4. Case I. Barium enema, postevacuation study 6 weeks later. Appendiceal abscess is no longer demonstrable. Note medially directed, angular, stiffened appendix with persistent evidence of narrowing at base (arrow) and adjacent cecal deformity.

days; since then bowel action had been normal. Although anorexia was present, there was no melena, vomiting nor significant weight loss. At the time of admission, abdominal examination showed no evidence of distention or abnormal mass. There were no areas of tenderness to palpation. Rectal and sigmoidoscopic examinations were negative. Temperature was 98.6°F., pulse 84, and respiration 20. The white blood cell count was 7,725 with 74 per cent neutrophils. Barium enema examination revealed contrast material to pass freely through the colon as far as the upper part of the ascending colon where extravasation occurred into an irregularly shaped cavity on the medial aspect of the colon. The cavity measured approximately 8×6 cm. and showed no variation in outline. It was located posteriorly and appeared fixed, the ascending colon and cecum moving freely over it (Fig. 5). The fistulous communication between it and the colon was easily visualized

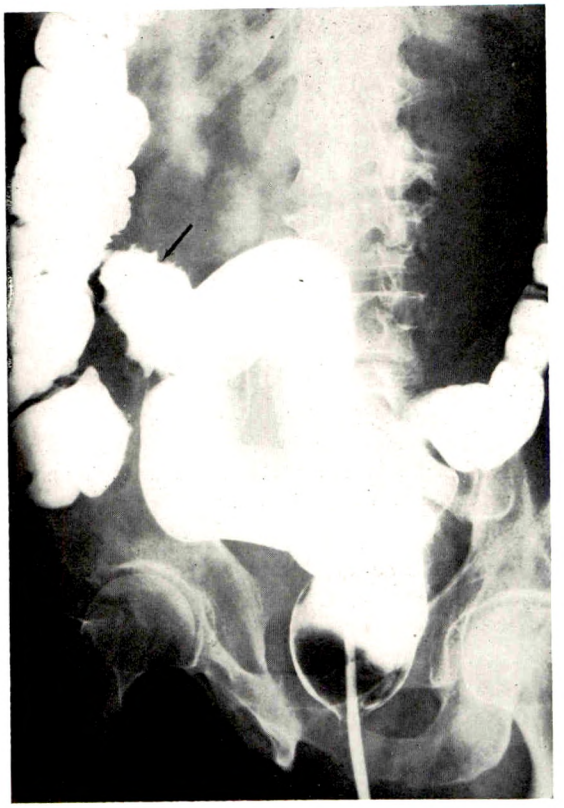


Fig. 5. Case II. Barium enema examination showing extraluminal extravasation (appendiceal abscess) arising medial to ascending colon.

roentgenographically (Fig. 6). The cecum filled well and showed no evidence of neoplasm. In the region of the extravasated barium there was a slight serrated concavity on the medial wall of the ascending colon, suggesting extrinsic pressure. On the postevacuation roentgenogram, the terminal ileum filled well and showed

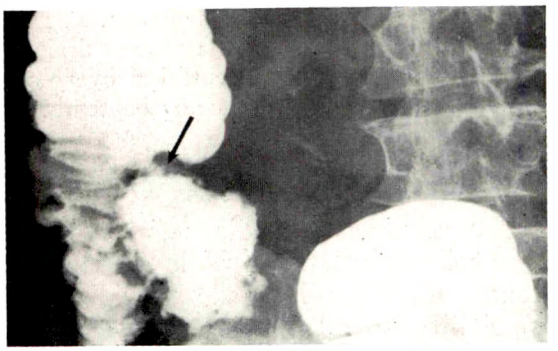


Fig. 6. Case II. Spot roentgenogram demonstrating fistula between appendiceal abscess and ascending colon.

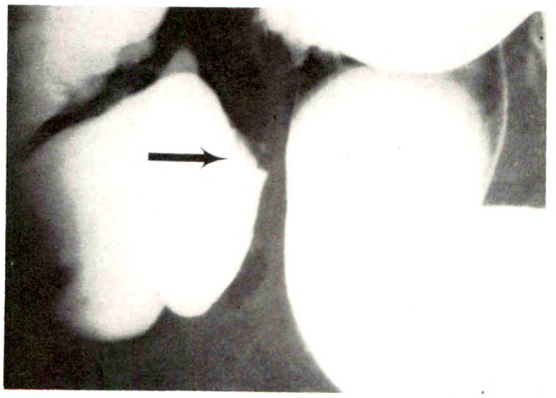


FIG. 7. Case II. Magnified view of appendiceal area showing shallow concave impression on cecum and intraluminal barium within the edematous base of the vermiform appendix.

no evidence of fistulation or other connection with the cavity. One roentgenogram demonstrated a shallow concave impression on the cecum with a small collection of barium adjacent to it. This was interpreted as being a small fleck of barium in the edematous base of the appendix (Fig. 7). The remainder of the appendix was not visualized. The roentgen diagnosis of a retrocecal appendiceal abscess with secondary rupture into the ascending colon was made. Following a short period of conservative treatment, operation was carried out on August 28, 1961. Laparotomy disclosed the cecum to be firmly adherent to the parietal peritoneum. The appendix was retrocecal in position, angulated, and had previously perforated at the convexity of the angulation. There was marked inflammatory reaction and fibrosis in this area, and a small abscess cavity was found which contained white fluid. The fluid was negative on culture. No other abnormality was noted in the abdomen. The appendix was removed and the abscess drained. The patient made an uneventful recovery and was discharged symptom free on September 9, 1961.

DISCUSSION

The roentgenologic diagnosis of appendico-colic fistulation, while rarely encountered, is easily made providing the possibility is kept in mind. Although such fistulation could conceivably occur into any section of the alimentary tract, it is probable that the two most likely colonic areas to be affected are the ascending and sigmoidal portions. Retrocecal positioning of the vermiform appendix obviously predisposes to localization of abscess formation and subsequent fistulation into regional structures. Evacuation of the contents of appendiceal abscess into the colon at the time of fistulation would appear to explain the sudden relief of pain, subsequent mild symptoms, and absence of leukocytosis.

Although the discovery of an abscess and an associated fistula into the ascending colon is likely to lead to consideration of the appendix as a possible site of origin, a similar involvement of the sigmoid colon, as in Case I, may be difficult to assess etiologically. However, in both cases, two features were helpful in incriminating the appendix as the site of original disease. First, there was no apparent primary colonic disease likely to lead to fistulation. Although several small diverticula were present in the descending colon in Case I, no definite evidence of diverticulosis was present in the sigmoid area. Secondly, changes were visualized in the vermiform appendix itself. It is interesting that in both cases the appendix was visualized either completely or in part, and its appearance and that of the cecum showed certain similarities. A concave filling defect of the cecum at the site of attachment of the appendix was observed. In addition, the proximal part of the appendix outlined by contrast material appeared narrowed. The attenuation of the vermiform appendix was apparently attributable to intramural edema. When the appendix was almost completely opacified (Case I), it appeared straightened and fixed with its tip directed toward the fistulated area adjacent to the sigmoid colon.

It is suggested that a careful scrutiny of the appendix be made in a search for roentgenologic evidence suggesting the presence of appendico-colic fistulation whenever extravasation of barium from

the colon is encountered and no other obvious colonic pathology is present.

SUMMARY

Two cases of appendico-colic fistula diagnosed preoperatively have been presented. In both cases extra-alimentary extravasations of contrast medium were encountered on barium enema studies. These communicated in one instance with the sigmoid colon and in the other with the ascending colon. In both cases, a careful scrutiny of the appendiceal area afforded indication that the source of abscess formation most likely arose initially as a result of acute retrocecal appendicitis with rupture, abscess formation, and subsequent fistulation into the large bowel.

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METASTASES TO THE GASTROINTESTINAL TRACT FROM MALIGNANT MELANOMA*

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THE tendency of malignant melanoma to metastasize widely is responsible for a variety of clinical and roentgen manifestations. The primary tumor frequently remains inconspicuous even though evidence of metastatic disease may be quite apparent. Metastatic involvement of the gastrointestinal tract by this tumor is not rare. It may be manifested clinically by intestinal hemorrhage or obstruction. The following cases are presented to demonstrate some of the features of metastatic melanoma in the stomach and small intestine, with emphasis on a roentgen finding which may aid in its diagnosis.

REPORT OF CASES

CASE I. This 54 year old white male was admitted to the Cincinnati Veterans Administration Hospital on April 19, 1961. He was referred because of epigastric and right upper quadrant pain and weight loss of 50 pounds during the previous 2 months.

A malignant melanoma had been removed from his left shoulder $2\frac{1}{2}$ years earlier. During the 5 months prior to admission, he had noted recurrent episodes of abdominal pain, occasional hemoptysis and melena, and progressive left-sided weakness. More recently, a nontender mass appeared in the left axilla.

Physical examination showed a mentally confused man with normal vital signs. Bronchial breath sounds were heard at the base of the right hemithorax. Examination of the abdomen revealed hepatomegaly and epigastric tenderness. Rectal examination was normal. A number of hard subcutaneous nodules were distributed over the left forearm, the thorax, and the abdomen. A large nontender lymph node was palpable in the left axilla. Expressive dysphasia, generalized left-sided weakness with flaccid paralysis of the left lower extremity, positive Babinski and Hoffmann signs on the left, and left-sided hypalgesia distributed over L4 to S1 were noted.

Positive laboratory findings included a hematocrit of 34 per cent, hemoglobin 10.7 gm., stool guaiac 4 plus, and urine melanin 3 plus.

Roentgen Findings. Chest examination revealed a large nodular lesion in the right lower lobe, interpreted as a metastasis. Upper gastrointestinal and small bowel series demonstrated multiple filling defects in the stomach and duodenum. Many showed a large central collection of barium, thought to indicate ulceration (Fig. 1, *A* and *B*; and 2). Less numerous polypoid defects were present in the jejunum and ileum, some of which also appeared ulcerated. In addition, a large polypoid mass was seen in the second portion of the duodenum and in the jejunum.

Biopsy of several of the subcutaneous nodules showed malignant melanoma. The patient's status deteriorated rapidly and he expired on the twenty-second hospital day.

Autopsy. There were widespread metastases involving the lower lobe of the right lung, myocardium, pleura, thyroid, liver, gallbladder, pancreas, left testis, adrenals, numerous lymph nodes, cerebrum, and gastrointestinal tract. There were numerous serosal and mucosal lesions in the stomach, duodenum, jejunum, and ileum. The mucosal lesions were, for the most part, well-circumscribed sessile nodules, some of which contained a large central depression. This represented ulceration in some and central umbilication with intact mucosa in others. Each neoplastic nodule appeared to extend into the muscular layer. There was an intussusception in the upper ileum, 9 cm. in length, with a large leading tumor mass. No lesions were found in the large intestine. Microscopic sections of the tumor nodules revealed malignant melanoma.

CASE II. This 30 year old white male was first admitted to the Jewish Hospital in October, 1957, with a pigmented lesion of the skin of

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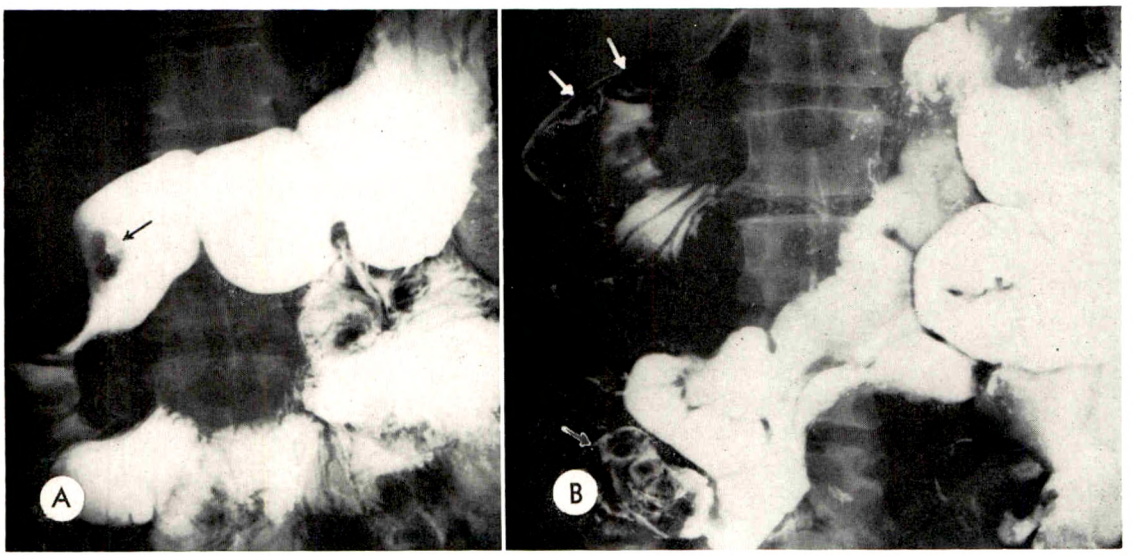


FIG. 1. Case 1. (*A*) Bulls-eye lesions of duodenal bulb (arrow). (*B*) Double contrast profile appearance of ulcerated lesions (upper arrows). Compare with Figure 4, *B* and *C*. Note additional nonulcerated polypoid lesions and intramural defect on the small bowel (lower arrow).

the midportion of the calf of the right leg, 3 cm. in diameter. It was excised widely and histologically revealed malignant melanoma. He was again admitted in October, 1958, with recurrence at the site of the previous operation and a second excision was performed. Malignant melanoma was again demonstrated. In April, 1960, a right supracondylar amputation and radical groin dissection were carried out for metastases. Tests for melanin in the urine were positive at this time.

In November, 1960, he was readmitted with a history of 15 pound weight loss, weakness, anorexia, and diffuse abdominal pain sometimes relieved by food ingestion. The physical examination was nonrevealing except for evidence of pallor and weight loss. The red blood cell count was 3.26 million, the hemoglobin 7.8 gm. Stools were positive for occult blood.

Roentgen Findings. Examination of the chest disclosed many metastatic nodules in both lungs. The upper gastrointestinal and small bowel series revealed numerous filling defects in the stomach and the small bowel. Several contained large collections of barium which were thought to represent ulcerations (Fig. 3).

Clinical Course. In January, 1961, the pa-

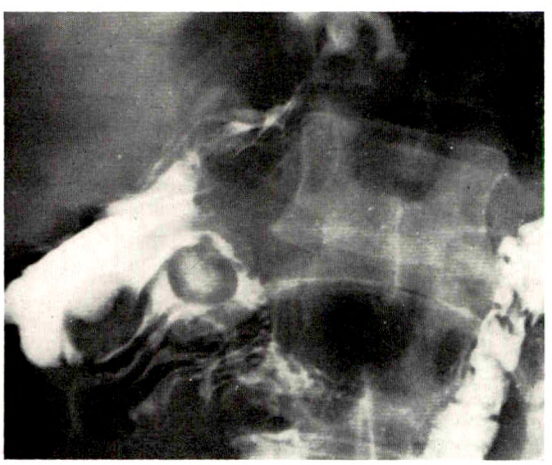


FIG. 2. Case 1. Bulls-eye lesions of the duodenum and stomach.

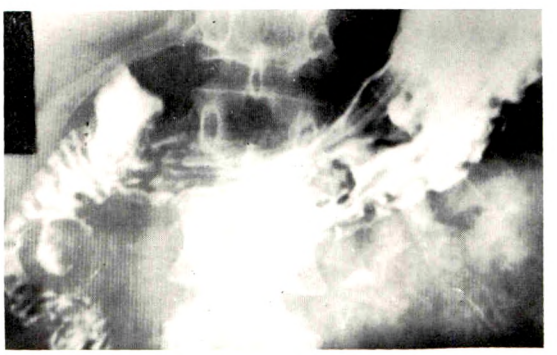


FIG. 3. Case 11. Ulcerated and nonulcerated polypoid lesions of the stomach. Note the bulls-eye lesion in the descending duodenum.

tient was re-admitted because of extreme weakness, nausea and vomiting. Chest roentgenograms taken at this time showed an increase in the number of metastatic pulmonary lesions. Upper gastrointestinal and small bowel series again revealed multiple filling defects, some with central ulceration. He expired at home in June, 1961. No autopsy was obtained.

Case III. This 32 year old white male was admitted to the Cincinnati Veterans Administration Hospital in December, 1961. He had been followed in the outpatient department of another hospital because of upper abdominal pain, vomiting, the presence of subcutaneous nodules of the thorax, and an enlarged left axillary lymph node. Biopsies of the skin and axillary lymph node revealed malignant melanoma.

Physical examination showed a chronically ill malnourished individual. Enlarged firm nontender cervical, axillary, and inguinal lymph nodes were palpable. Several hard subcutaneous nodules were scattered over the left hemithorax. The upper abdomen was tender and the liver was enlarged.

Positive laboratory findings included a hemoglobin of 8.5 gm., hematocrit of 30 per cent, and red blood cell count of 3.26 million.

Roentgen Findings. Chest roentgenograms revealed multiple bilateral pulmonary metastases and a pleural effusion on the right. Examination of the gastrointestinal tract was not performed because of the patient's poor condition. He expired on the tenth hospital day.

Autopsy. There were widespread metastases involving the lung, peritoneum, retroperitoneal space, pancreas, adrenals, and numerous lymph nodes. Examination of the stomach showed the entire mucosa to be studded with numerous large well-delineated tumor nodules, the majority of which showed central ulceration. Other nodules revealed varying degrees of umbilication without ulceration. Similar lesions were present in the duodenum. The jejunum and ileum contained numerous nodules, but none of these were either umbilicated or ulcerated. The colon was free of disease. Microscopic sections of the nodules were consistent with malignant melanoma.

DISCUSSION

The occurrence of multiple metastases in the stomach and intestines in patients with malignant melanoma has been well-documented.[1,2,5,8–12] The large bowel is usually entirely spared, as in the present cases. According to Willis,[14] who collected 45 cases from the literature, the metastatic lesions in the intestines are found in decreasing number from the proximal to the distal portions of the affected gut.

Pathologically, the metastatic tumors may be in the form of well-circumscribed round or oval nodules, plaques, or sessile or pedunculated polypoid masses. The nodules or plaques appear to stem from submucosal infiltration which may extend to the muscularis and mucosa, while the polypoid lesions appear to arise in the mucosa itself. All these forms of lesions are commonly found to coexist. Ulcerations, when present, are central and relatively large. Some nodules may be centrally umbilicated without actual ulceration. The formation of an enlarging pedunculated mass projecting into the bowel lumen may lead to intussusception.

Melanomatous involvement of the stomach may be solitary or multiple.[1,3,4,5,7,11,12] The case reports of gastric involvement indicate a predominance of ulcerating lesions.

ROENTGEN FINDINGS

Richman and Lipsay,[12] in their review of 33 cases of gastrointestinal metastases from melanoma, including 2 of their own, emphasized the presence of polypoid gastric and intestinal filling defects. A number of cases of solitary ulcerated gastric metastasis has been reported.[1,6,7] Although polypoid lesions in the small intestine have been described, ulceration within them has not been previously mentioned.

The most striking roentgen findings are the multiplicity of the lesions and the large collection of barium within them. The latter often results in a "bulls-eye" or "target" appearance (Fig. 1*A*; 2; and 3). As mentioned earlier, these may result from either ulceration or epithelialized umbilication. Calderon, Ceballos and McGraw[3] demonstrated a gastric lesion with this appearance which pathologically coincided

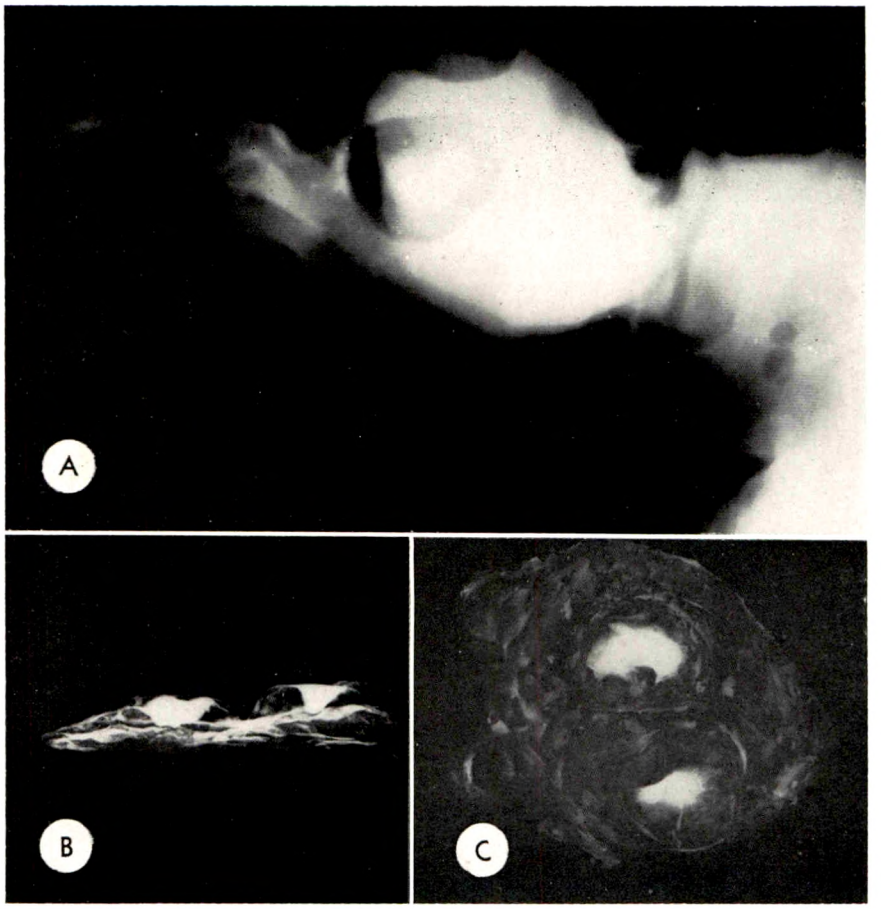


Fig. 4. (*A*) Bulls-eye images as they appear in the duodenum in the autopsy specimen of Case 1. The lumen was filled with barium. *B* and *C* are frontal and lateral projections of individually barium-coated lesions from the same specimen, demonstrating the gross morphology of the lesions shown in Figure 5.

with a nonulcerated centrally umbilicated nodule. There is close correlation of the roentgen image with the gross morphology of the lesions seen in the autopsy specimens (Fig. 4, *A–C*; 5; and 6, *A–D*). Because of the widespread metastatic involvement of neighboring viscera, extrinsic pressure defects on the intestinal tract are also common. Intussusception may lead to partial or complete intestinal obstruction.

Briefly stated, then, the gastrointestinal roentgen signs of metastatic melanoma are: (1) multiple intraluminal and intramural defects, often presenting a bulls-eye or target appearance; (2) extrinsic pressure defects from involvement of adjacent organs; and (3) intussusception.



Fig. 5. Case 1. Autopsy specimen of duodenum showing sessile nodular lesions some of which have a central ulceration while others do not (arrows).

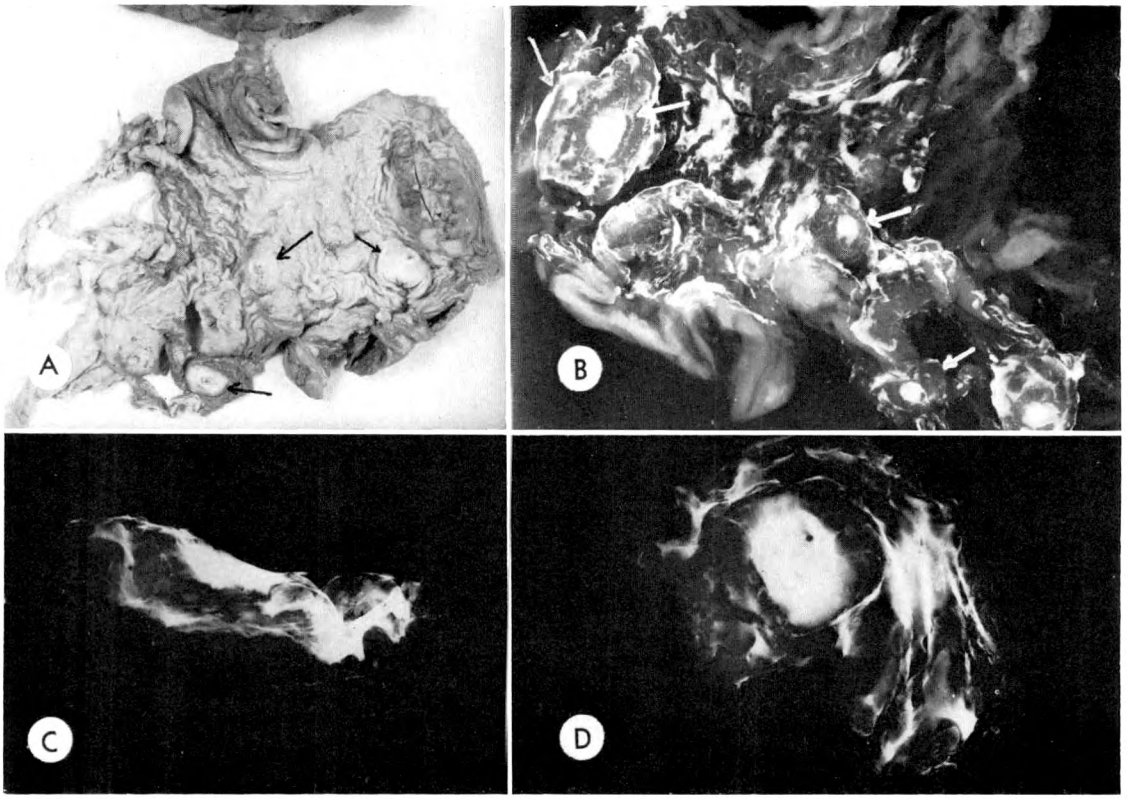


Fig. 6. Case III. (*A*) Bulls-eye lesions of the stomach as shown in the specimen (black arrows). (*B*, *C* and *D*) Appearance of these lesions after barium coating (white arrows).

DIFFERENTIAL DIAGNOSIS

We consider the multiple bulls-eye or target lesions in the gastrointestinal tract to be highly suggestive of metastatic melanoma. Single lesions of this type may also be seen with such diverse entities as spindle cell tumor, lymphoma, aberrant pancreas, carcinoid, granuloma with eosinophils, Kaposi's sarcoma, and even carcinoma. However, multiplicity of the target lesions is rare among this group, except perhaps for Kaposi's sarcoma. A case of Hodgkins' disease with multiple bulls-eye lesions of the stomach has recently come to our attention. In melanoma the ulceration is rather large in relation to the over-all diameter of the lesion. The index of suspicion of melanoma is further increased if the lesions are distributed in both the stomach and small bowel. In a patient with a known primary melanoma, the presence of bulls-eye gastrointestinal lesions is pathognomonic of metastatic melanoma.

SUMMARY

Three cases of metastatic melanoma of the gastrointestinal tract are presented, and the clinical features and pathologic findings are briefly reviewed. Characteristic roentgen features are reported. Emphasis is placed on the demonstration of multiple "bulls-eye" or "target" lesions. The differential diagnosis of these lesions is discussed.

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ESOPHAGEAL MONILIASIS*

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PROLONGED use of antimicrobial and steroid therapy predisposes to disseminated moniliasis by permitting overgrowth of the normal intestinal flora and by diminishing the defense of the skin and mucous membranes against mycotic agents. The virulence of monilial infections has been enhanced by these mechanisms.[3,11,13,17] Esophageal moniliasis is a serious illness and unless identified and treated early can be progressive and fatal. However, when so recognized it may be relatively benign and reversal of symptoms can be achieved by adequate treatment.[10,16]

Only 3 instances of esophageal candidiasis showing diagnostic roentgenographic changes and verified at necropsy have been reported (see Table 1). An additional case report is presented:

REPORT OF A CASE

A 43 year old white female was first hospitalized because of weakness, palpitation, and shortness of breath. She was in acute distress, and had marked pallor, stomatitis, and a huge necrotic ulcer on her hard palate. A clinical diagnosis of acute leukemia was made. She was known to have had tuberculosis of the right upper lobe, treated with apparent success by pneumothorax. Antileukemic treatment was begun with blood transfusions, steroids, together with antituberculosis therapy (streptomycin and INH) to combat reactivation of the tuberculosis. A temporary remission was obtained and the patient was discharged after 3 weeks.

She was readmitted 3 months later, acutely ill and complaining of weakness and lassitude. Two weeks before, she had been treated for an upper respiratory infection with a broad spectrum antibiotic. Pertinent physical findings were marked pallor, a diffuse erythematous maculo-papular rash over her trunk, upper arms and thighs and bilateral axillary lymphadenopathies. An area of thrush was present on the right buccal mucosa. A chest roentgenogram showed calcified tuberculous foci in both lung apices and an infiltrate in the anteroinferior segment of the right upper lobe. Antituberculous drugs, steroids and several blood transfusions were again administered.

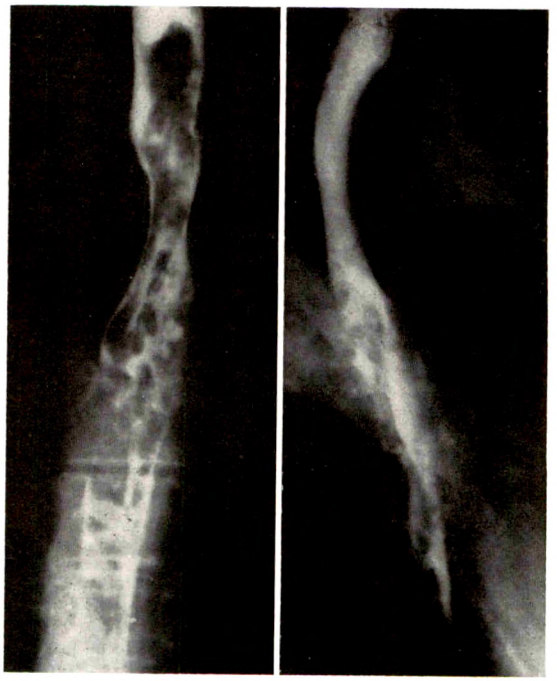


FIG. 1. Examination of the esophagus shows slow passage of the contrast medium (barium paste). The spot roentgenograms permit identification of the coarse, irregular, granular density of the esophageal mucosa.

One week after admission, her temperature rose to 101° F. She complained of right precordial and substernal pain, especially when swallowing. Because of progressively increasing dysphagia, roentgenographic examination of the esophagus was performed. The esophagram showed an atypical appearance of the middle third of the esophagus. The mucosa was thickened and coarsely irregular, suggesting the presence of ulcerative lesions (Fig. 1).

Diagnostic bronchoesophagoscopy revealed a firm, whitish-yellow exudate which adhered to and covered almost the entire length of the mid-

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esophagus on its right lateral wall. Removal of the exudate caused bleeding from the base, where the mucosa was found to be eroded and raw. Histopathologic and microbiologic studies showed necrotic squamous mucosa with fungal (monilial) and bacterial growth. Bronchial washings showed only some fibrin and inflammatory cells. The oral thrush was still present and the patient received a course of treatment with amphotericin B (Fungizone).

In spite of all therapeutic endeavors the patient had a progressively downhill course, with increasing dysphagia, weakness and fever. Her condition was further complicated by the appearance of an esophageal-cutaneous fistula shortly after diagnostic bronchoesophagoscopy had been performed. She expired on the forty-eighth hospital day.

At necropsy a cutaneous fistula to the esophagus was observed. There was extensive inflammatory change in the esophagus, together with multiple erosions, intramural hemorrhage, and extensive mucosal necrosis. A thick, whitish-yellow pseudomembrane composed of monilia and debris was present.

COMMENT

In esophageal moniliasis the changes on roentgenologic examination of the esophagus are principally irritability and spasticity of the involved portion, together with extensive mural changes. An irregular, ragged esophageal outline, often containing a myriad of small filling defects, reflects destruction of the mucous membrane. The longitudinal folds may still be discernible and some distensibility of the esophagus may be present. However, in advanced or untreated cases, marked narrowing of the lumen of the esophagus occurs.[1,2,4,7,8,9,10,12] In early cases the esophageal changes show rapid improvement following antifungal therapy and within a few days roentgenograms may reveal a normal esophagus, although residual irritability can persist for a week or more.

Esophageal moniliasis produces a mucosa which has a bizarre granular, cobblestone appearance. This may be limited to a relatively short segment or extend throughout the length of the esophagus. This appearance is due to a pseudomembranous lining, consisting of monilia and debris. Hyperemia, edema and inflammation of the deeper layers are associated with mucosal ulceration.[10]

It is of interest to note the increased incidence of esophageal moniliasis in patients suffering from chronic blood dyscrasias.[1,4,8,9,10,15] The present case adds evidence

Table I

ROENTGENOGRAPHIC CHANGES IN MONILIAL ESOPHAGITIS

Authors	Total Patients	Age and Sex	Pre-Existing Conditions	Therapy	Signs and Symptoms	Roentgenographic Findings	Necropsy Findings
Andren and Theander[1] (1956)	1	Adult	Leukopenia, splenomegaly, severe recurrent infections	Antibiotics, ACTH and cortisone	Oral thrush, severe dysphagia	Irregular, jagged esophageal outline; extensive loss of mucosal pattern	Ulcerated esophageal mucosa lined with pliable yellow pseudomembrane (*C. albicans* cultured)
Kaufman and Levene[9] (1958)	1	16 M	Acute lymphatic leukemia	ACTH, radiation to spleen	Epigastric and substernal pain on swallowing	Irritability, irregularity and loss of mucosal pattern; narrowing of lumen; absence of peristalsis	Thick, yellowish pseudomembrane (monilia and debris); ulceration and necrosis of mucosa
Kaufman[8] (1958)	1	4 M	Aplastic anemia	Cortisone, prednisone, erythromycin, chloramphenicol, penicillin, polymyxin, streptomycin	Abdominal pain, rectal bleeding	Marked irregularity of mucosal outline with filling defects of various size and shape throughout thoracic esophagus	Irregular ulcerated esophageal mucosa; extensive intramural hemorrhages (*C. albicans* cultured)

for this and also emphasizes the risks and problems associated with prolonged administration of antimicrobials and steroids.

If the heralding signs of oral thrush and dysphagia appear in a chronically ill patient receiving such therapy, the diagnosis of esophageal moniliasis should be considered. Only by establishing the diagnosis as early as possible can proper and judicious therapy be instituted with some hope of reducing the morbidity and mortality of this condition.

SUMMARY

An adult female patient under treatment for leukemia and tuberculosis developed esophageal moniliasis with progressing dysphagia. Roentgenographic examination revealed marked spasm and irregularity of the mucosal pattern of the middle third of the esophagus. This was shown at esophagoscopy, and later at necropsy, to be due to an ulcerative pseudomembranous process, produced by a thick growth of *C. albicans*. Early detection and treatment of esophageal moniliasis is important if relief is to be obtained.

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IS SURGICAL REMOVAL OF EVERY COLONIC POLYP NECESSARY?*

By LEO S. FIGIEL, M.D., STEVEN J. FIGIEL, M.D., *and* FRED K. WIETERSEN, M.D.
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IT IS generally assumed that most colonic carcinomas are the result of malignant change in a benign colonic polyp. On this premise, until recently, most authorities advocated surgical removal of all colonic polyps including those beyond the reach of the endoscope. The rule that "every polyp is a potential cancer" was applied widely and little consideration was given to such factors as the age of the patient, the size of the polyp, or the statistical evaluation of the surgical risk to the patient as measured against the risk of carcinogenesis, if the patient remained untreated.

The data published by Arminski and McLean,[1,2] Feyrter,[6] Helwig,[17] Hultborn,[18,19] Grinnell and Lane,[13] and Spratt *et al.*[25,26,27] are of greatest interest in this respect and indicate a necessity for re-evaluation of formerly accepted concepts and conclusions. A sounder rationale for the treatment of the patient with one or more colonic polyps beyond the reach of the endoscope can be formulated after study of the data accumulated by these authors.

INCIDENCE OF MALIGNANCY IN POLYPS

The vast majority of colonic polyps are benign lesions. Of polyps smaller than 1 cm. in size, only 2 per cent or less show evidence of malignancy on histopathologic study.[1,13,27]

INCIDENCE OF POLYPS

There is a substantial variation in the percentage figures of the incidence of polyps cited in various autopsy reports, due principally to the age groups studied. The detailed work of Feyrter[6] and Arminski,[2] correlating the incidence of the colonic polyps with age, establishes a frequency rate of at least 50 per cent or more for people over the age of 60. In other words 1 out of every 2 patients over the age of 60 harbors one or more colonic polyps. In Arminski's[2] study of 1,000 autopsy cases this figure applies only to adenomatous and papillomatous polyps and excludes other histologic types.

This problem is further complicated by the multiplicity of polyps. Numerous authors state that 15 to 50 per cent of patients with polyps have multiple lesions. Feyrter's[6] series of 1,800 autopsies included 386 cases with a total of 1,017 polyps. The figures cited by Arminski[2] indicate that 46.5 per cent of the autopsy cases in his series had 2 or more polyps.

LOCATION OF POLYPS

The autopsy studies of Feyrter,[6] supported by Hultborn's[18] small series, indicate that 20 per cent or less of all colonic polyps present in their material were found in the extraperitoneal portion of the rectum, that is, below the rectosigmoid junction. Arminski[2] cites a figure of 18.8 per cent for rectal polyps in his autopsy series. He noted an equal distribution of colonic polyps between the right and left halves of the colon when the rectum is excluded (the mid-transverse colon constitutes the dividing line for right and left halves). This observation is supported roentgenographically by using high kilovoltage compression techniques.

REPORT OF CASES

CASE 1 (Fig. 1, *A*, *B* and *C*). W.M., a 39 year old white male, was admitted on September 7, 1958 with persistent epigastric pain which was relieved by food intake and alkalis. Six years previously, according to the patient's history, a small malignant polyp of the rectum was removed at another hospital. This patient

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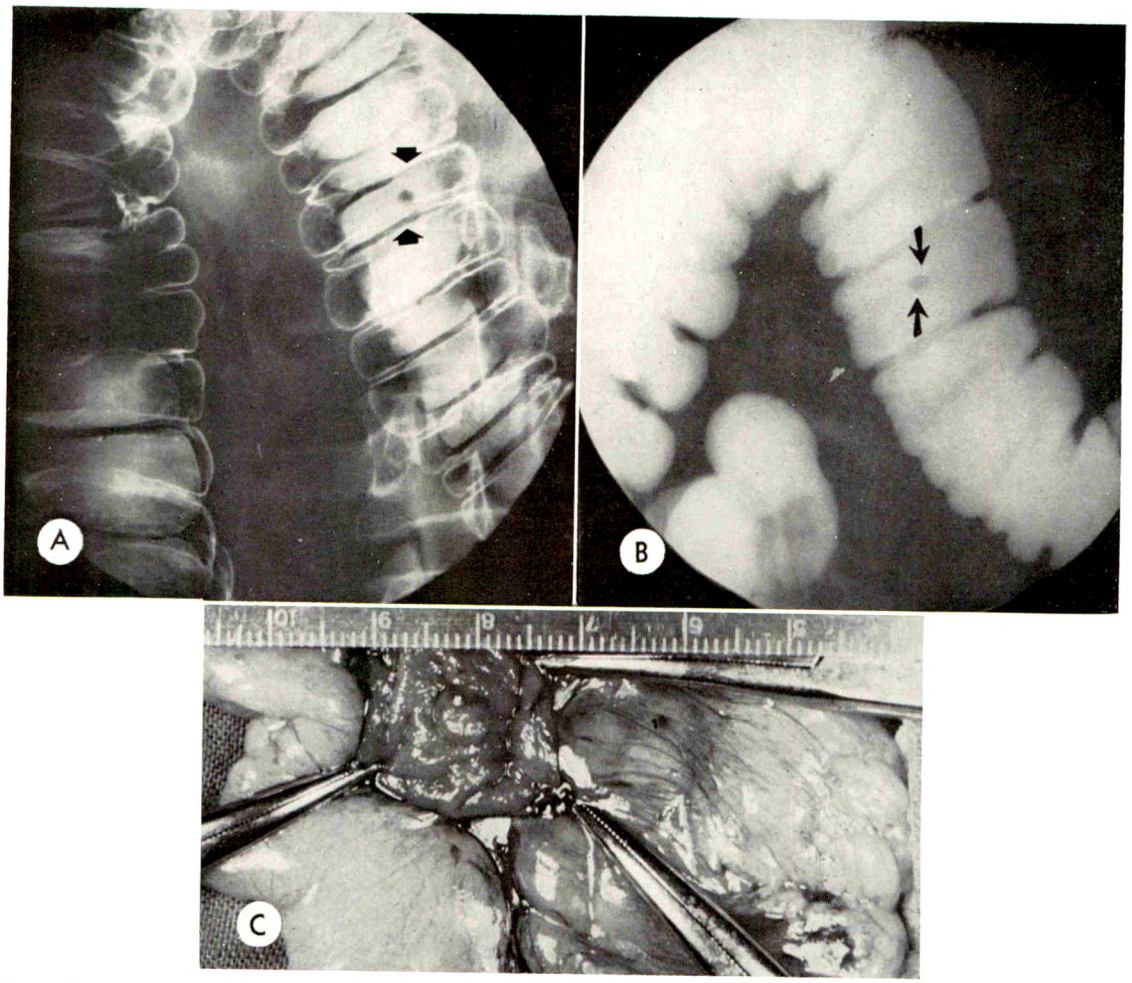


FIG. 1. Case I. (*A*) A 4 mm. polypoid lesion in the proximal transverse colon was visualized on an air contrast study in 1953. (*B*) Follow-up study with a high kilovoltage compression technique in 1958 demonstrated no change in the size of this lesion. (*C*) Operative specimen demonstrating a small sessile 4 mm. lesion which on histologic study proved to be a benign adenomatous polyp.

was admitted for gastric resection because of a symptomatic duodenal ulcer with roentgenographic demonstration of a moderate sliding hiatus hernia, deformity of the duodenal bulb, and a 1 cm. prepyloric gastric polyp.

In 1953 a 4 mm. polypoid lesion of the proximal transverse colon was discovered. Yearly follow-up examinations over a period of approximately 5 years revealed no change of any type in the size of this lesion. Surgery on September 10, 1958 consisted of repair of the hiatus hernia, a subtotal gastric resection with vagotomy and a local excision of the colonic polyp after colotomy. The patient had an uneventful recovery.

Comment. This case is noteworthy because an approximate 5 year follow-up revealed no change in the size or shape of a 4 mm. polypoid lesion in the proximal transverse colon. On this basis it was our impression that this was a benign polyp. Histologic studies confirmed this impression with the pathologist reporting a benign adenomatous polyp.

CASE II (Fig. 2, *A* and *B*). W.H., a 39 year old white female, was admitted on November 11, 1959 because she passed bright red blood rectally on numerous occasions. Early in 1955 this patient was examined at a Cancer Clinic in Detroit, because of rectal bleeding. Four small rectal polyps were removed. A 10×15 mm. polyp was found in the proximal de-

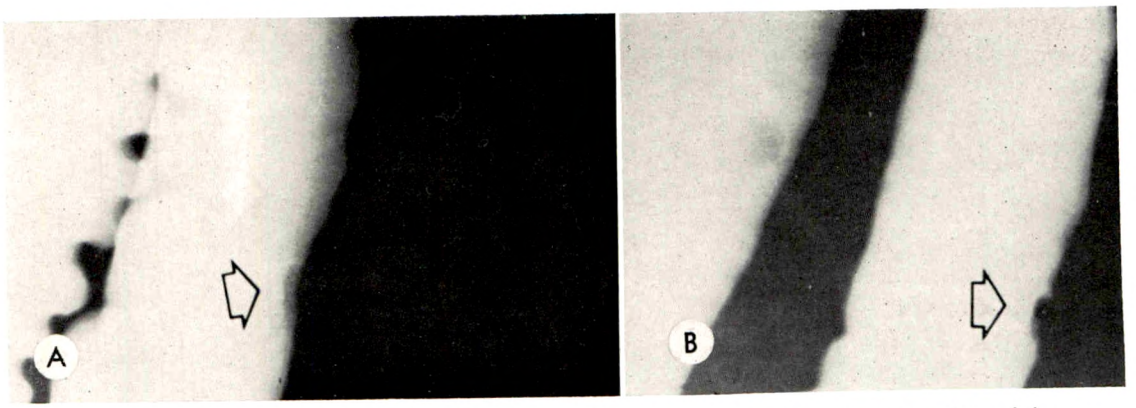


FIG. 2. Case II. (*A* and *B*) Six year follow-up studies of a small sessile 3×7 mm. polyp of the mid-descending colon, which proved to be a benign adenoma.

scending colon on barium enema study. This lesion was excised. The pathologist reported a benign adenomatous polyp.

Approximately one year later during a follow-up study, a small 3×7 mm. sessile lesion was discovered in the mid-descending colon. On retrospective study of the earlier roentgenograms of November, 1955, this lesion was noted to be present. Since this young patient was reluctant to undergo a second surgical procedure, a follow-up study was undertaken. During the next 3 years she had numerous episodes of rectal bleeding and had a hemorrhoidectomy in August, 1957. Small rectal polyps were removed on several occasions.

In September, 1961, a 10 mm. polyp was detected in the proximal sigmoid with no change being noted in the small sessile, 3×7 mm. lesion in the mid-descending colon. Surgery was deemed necessary and both lesions were removed. On histologic study both were proven to be benign adenomatous polyps.

Comment. We have included this case because of a 6 year follow-up of an extremely small sessile, 3×7 mm. polyp. No change in the size or shape of this lesion was demonstrated during this interval. This case proves that even the very smallest lesion can be followed accurately and simply with high kilovoltage compression techniques.

CASE III (Fig. 3, *A* and *B*). A.C., a 58 year old white female, was admitted for a general check-up examination with symptoms of generalized weakness, nausea, vomiting and prostration. The attending physician noted that she was a very nervous individual. Complete gastrointestinal studies on January 13 and 14, 1954 revealed a small, 11 mm. polyp in the mid-descending colon.

Comment. Progress roentgenographic studies have shown no change in the size or shape of the 11 mm. polypoid lesion of the descending colon in a period of almost 6 years. Absence of change indicates the presence of a benign polypoid lesion.

CASE IV (Fig. 4, *A* and *B*). H.M., a 59 year old white female, was admitted on April 28,

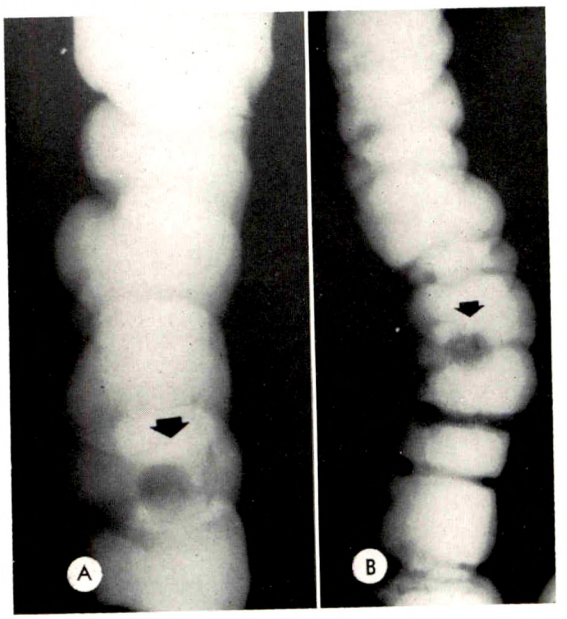


FIG. 3. Case III. (*A* and *B*) Six year follow-up studies of an 11 mm. polypoid lesion in the mid-descending colon showing no change in size. This is presumed to be a benign lesion.

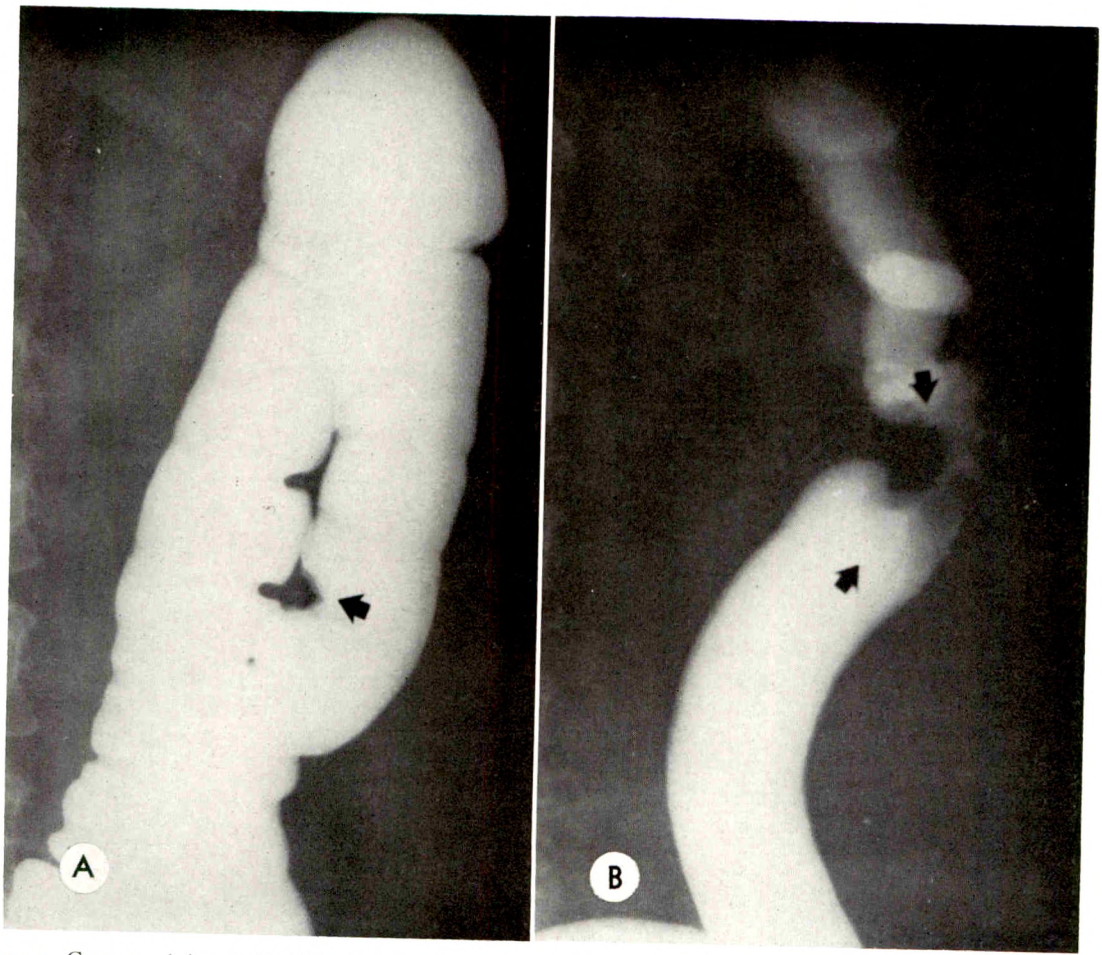


FIG. 4. Case IV. (*A* and *B*) Note the development of an annular constricting carcinoma of the proximal descending colon from a 1 cm. polypoid lesion in 2 years and 3 months.

1957 with a chief complaint of abdominal pain and diarrhea. The patient had a history of amebic dysentery in the late 1920's. No recurrences of this disease were noted during the last 10 to 12 years.

The patient stated that she felt well until approximately 2 to 4 years previously when, "she just didn't feel well—poor strength and indigestion." Barium enema examination on January 27, 1955 was reported normal. Early in 1956 the patient noted an occasional decrease in the caliber of the stool with dark red flecks in it. A barium enema examination at another hospital on May 10, 1956 was reported negative. In January, 1957 she had an acute attack of abdominal pain, diarrhea and vomiting, and passed several large amounts of bloody mucus in the stool. On April 20, 1957 a barium enema examination revealed an annular obstructing neoplasm in the proximal descending colon.

A left hemicolectomy for carcinoma was performed on April 2, 1957. The neoplasm extended through the wall of the intestine with metastases to the mesenteric lymph nodes.

Comment. Retrospective study of the barium enema roentgenograms of January 27, 1955 revealed a sessile lesion in the proximal descending colon which measured approximately 1 cm. in size. This is the exact site at which an annular constricting carcinoma was demonstrated in 1957. The interval between the earliest and last studies was 2 years and 3 months. During this period a 1 cm. polypoid lesion developed into a frank annular obstructing carcinoma.

CASE V (Fig. 5, *A*, *B* and *C*). L.C., a 69 year

old white female, was admitted on December 7, 1957 with a history of constipation and a weight loss of 16 pounds during the previous 10 months. There was microscopic evidence of blood loss. Physical examination revealed a palpable 3 cm., firm, but movable, mass in the right lower quadrant. Barium enema examination on November 27, 1957, done on an outpatient basis prior to admission, demonstrated a polypoid tumor of the mid-ascending colon.

A right hemicolectomy with ileotransverse colostomy was performed on December 10, 1957 for an adenocarcinoma Grade IV of the large intestine which had extended into the muscular layer with metastases to the regional lymph nodes. The patient was discharged after an uneventful course on December 21, 1957. Subsequent roentgenographic studies on October 20, 1960 revealed no abnormality of the anastomosis. The patient is in good health at this time.

Comment. Retrospective study of barium enema roentgenograms taken on June 14, 1955 and October 12, 1956 as well as a correlation with the study of November 27, 1957 showed the development of a frank polypoid neoplastic lesion from a polyp about 1 cm. in size. The interval from the small polypoid lesion to the gross polypoid cancer was approximately 2 years and 5 months. It is noteworthy that on the initial study of June 14, 1955 a sessile polypoid lesion of 10–12 mm. was demonstrable. In our experience if compression techniques had been utilized at that time, a demonstration of this lesion would have been possible and the patient would have been spared the subsequent development of a frank neoplastic lesion. We routinely take a high kilovoltage compression spot roentgenogram of the ileocecal region at the present. The studies of October 12, 1956 demonstrated a lesion which measured 3.5 cm. and which appeared to be quite obvious; however, it was overlooked. It is possible that this was misinterpreted as the ileocecal valve which can be identified more inferiorly.

Case VI (Fig. 6, *A*, *B*, and *C*). W.G., a 60 year old Negro male, was admitted on February 24, 1960 with chief complaints of fullness in the lower abdomen for 2 weeks and an 8 pound weight loss during the previous 3 weeks. The patient denied any change in bowel habits, melena or tarry stools. The physical examination revealed several scars in the right lower quadrant secondary to previous surgery in this region. Past history disclosed that a tumor of the colon was removed in 1950 at another hospital.

The hemoglobin was 14.2 gm., the red blood cell count 4,570,000 and the white blood cell count 7,300. A barium enema examination on February 23, 1960 revealed an annular constricting carcinoma of the cecum and suspicion of a 1 cm. polyp in the cecal base at its medial wall.

Palliative surgery of the right colon with an ileotransverse colostomy was performed on February 27, 1960. There were multiple

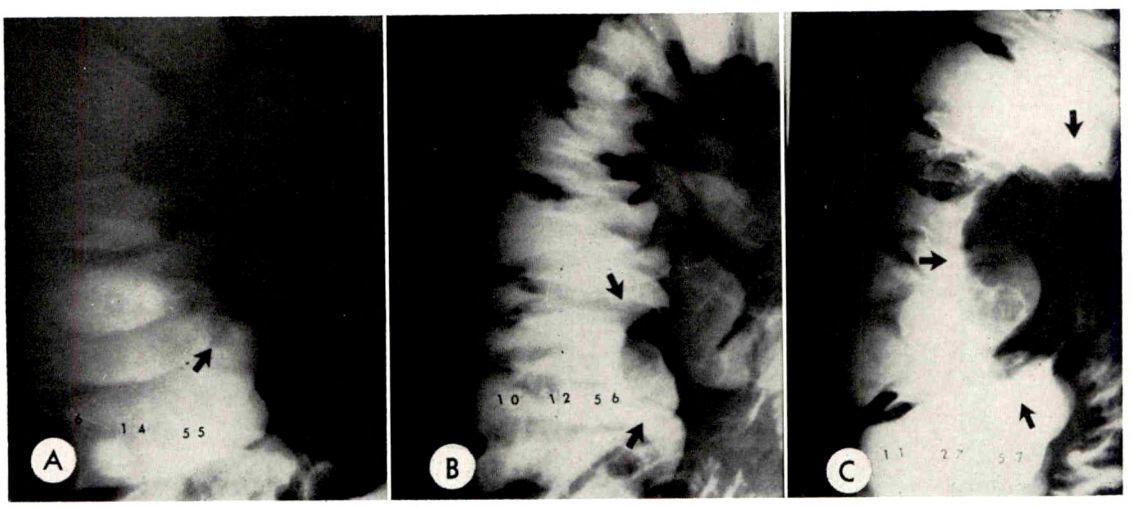


Fig. 5. Case v. (*A*, *B* and *C*) Note the development of a polypoid neoplasm of the ascending colon from a 10 to 12 mm. polypoid lesion in 2 years and 5 months.

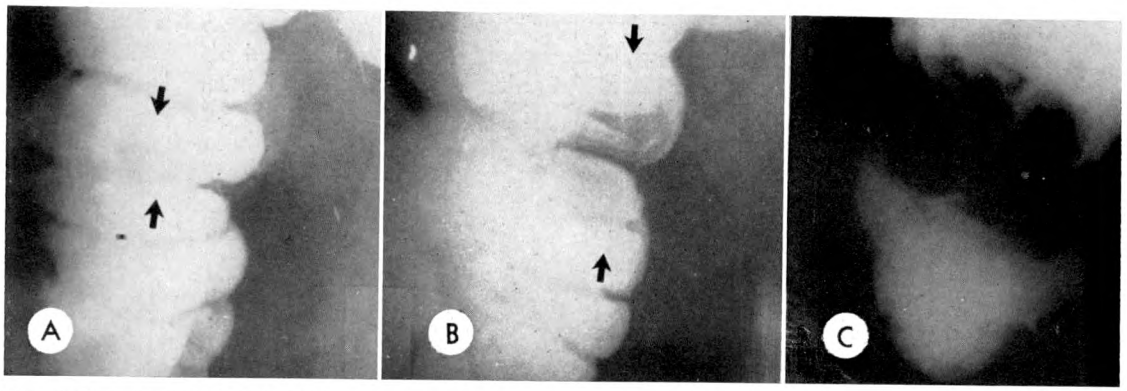


FIG. 6. Case VI. (*A*, *B* and *C*) Note the development of an annular concentric carcinoma of the cecum from a polypoid lesion of approximately 18 mm. in size in an interval of 3 years and 3 months.

metastases to the liver. The pathologist reported an adenocarcinoma infiltrating the intestinal wall with metastatic involvement of lymph nodes. A benign adenomatous polyp of approximately 1 cm. in size was present in the cecum.

Comment. We were able to obtain the previous records of this patient from another hospital. On reviewing the earlier barium enema studies of November 11, 1956 and October 15, 1958, clearly apparent polypoid defects were noted in the cecum at the level of the annular carcinoma which was demonstrated on our roentgenograms of February 23, 1960. The progression of growth from an 18 mm. polypoid lesion to the frank annular concentric carcinoma occurred in a period of 3 years and 3 months.

CASE VII (Fig. 7, *A*, *B* and *C*). A.L., a 70 year old white male, was admitted on November 20, 1958 for elective surgical removal of a pedunculated polyp in the mid-ascending colon. Ten years previously this patient had a laparotomy for intestinal obstruction with resection of a portion of the descending colon and splenic flexure for carcinoma. He has been completely asymptomatic since that time, having had numerous check-up examinations including 3 barium enema studies elsewhere.

A colotomy with resection of a 2.6 cm. pedunculated polyp which had a broad based attachment in the mid-ascending colon was performed on November 25, 1958. The pathologist reported a benign ademomatous polyp.

Comment. We were able to review all of the

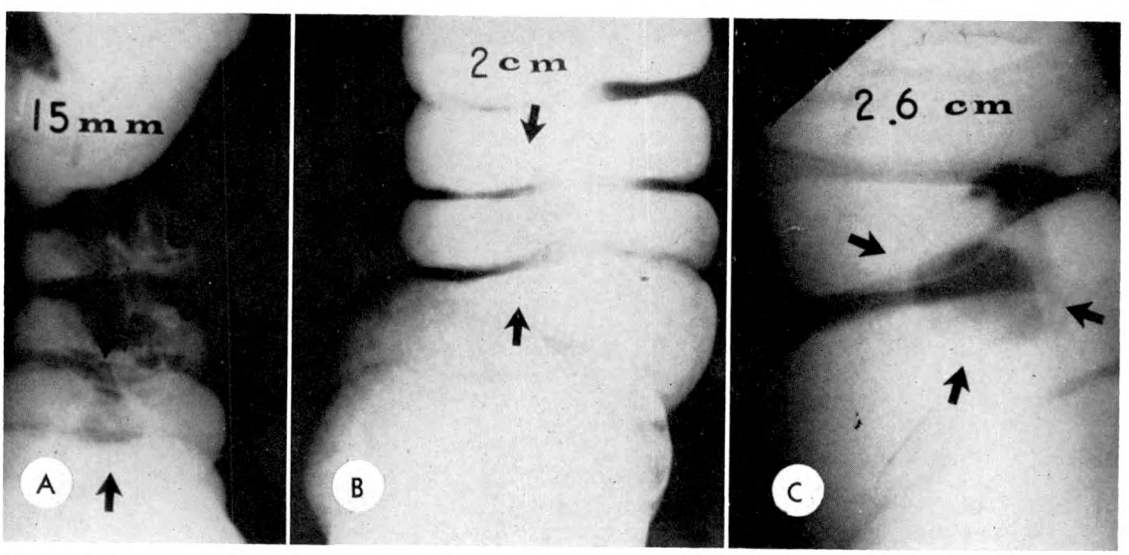


FIG. 7. Case VII. (*A*) 1.5 cm. polypoid lesion in the mid-ascending colon in 1951. (*B*) Polypoid lesion measuring 2 cm. at this site in 1955. (*C*) Pedunculated 2.6 cm. polyp demonstrated at this site with high kilovoltage compression technique in 1958.

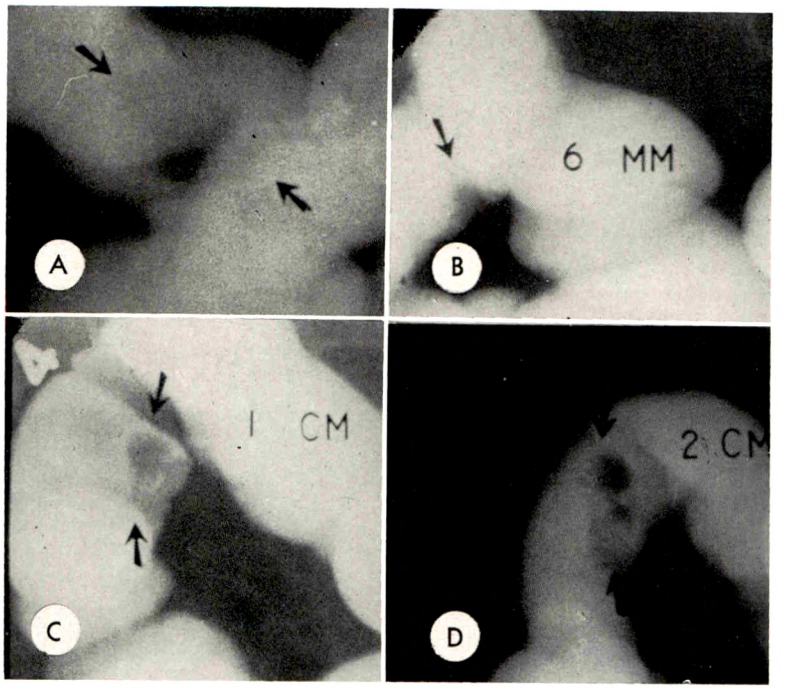


Fig. 8. Case VIII. (*A*) June 24, 1958: Sessile lesion measuring 18 mm. demonstrated in the mid-sigmoid colon. (*B*) April 8, 1959: Six month postoperative check-up demonstrating a small 6 mm. polypoid defect at the site of surgery. (*C*) October 7, 1959: Note the increase in size from 6 mm. to 1 cm. of the polypoid lesion. (*D*) January 21, 1960: Note further increase in size of the polyp which assumes a bilobulate appearance and measures 2 cm. in length. The growth of this polypoid lesion occurred in a 9 month period.

earlier barium enema roentgenograms of this patient. In 1951 a polyp of approximately 1.5 cm. was clearly visible in the mid-ascending colon with the study of 1955 faintly demonstrating this lesion which measured an estimated 2 cm. in size at that time. Our roentgenographic studies of 1958 clearly demonstrated a pedunculated lesion of 2.6 cm. In effect we have a 7 year follow-up of a polyp of the ascending colon increasing in size from 1.5 to 2.6 cm. over this period. On histologic study this was a benign adenomatous polyp.

Case VIII (Fig. 8, *A*, *B*, *C* and *D*). M.C., a 50 year old white female, was admitted with a complaint of tenderness in the right lower quadrant. Complete gastrointestinal studies demonstrated a sessile polypoid lesion in the sigmoid colon and a small polyp in the proximal transverse colon.

Colotomy openings in the sigmoid and transverse colon with removal of polyps were performed on October 2, 1958. The sigmoid polyp was reported as a benign adenomatous lesion and the polyp in the transverse colon was reported as an adenomatous polyp with invasive carcinoma. The patient was re-operated on October 13, 1958 with a resection of the transverse colon.

Postoperative barium enema studies on April 8, 1959, October 7, 1959 and January 21, 1960 demonstrated an increase in the size of a polypoid defect at the surgical site. On the initial studies of April 8, 1959 it was not possible to differentiate a small granuloma occurring at the site of surgery from a polypoid lesion; however, subsequent follow-up studies which demonstrated an increase in size definitely established the presence of a growing polypoid lesion. After several attempts at sigmoidoscopy, this lesion was reached and removed. Histologic study proved this lesion to be a benign adenomatous polyp.

Comment. This case is of considerable interest since 6 months following surgery a small sessile deformity was detected at the site of surgery. Follow-up studies demonstrated an increase in the size of this polypoid lesion from 6 mm. to 20 mm. in a period of approximately 9 months. This was proven to be a benign adenomatous polyp after surgical removal. Such a rapid rate of growth is extremely rare for a benign lesion

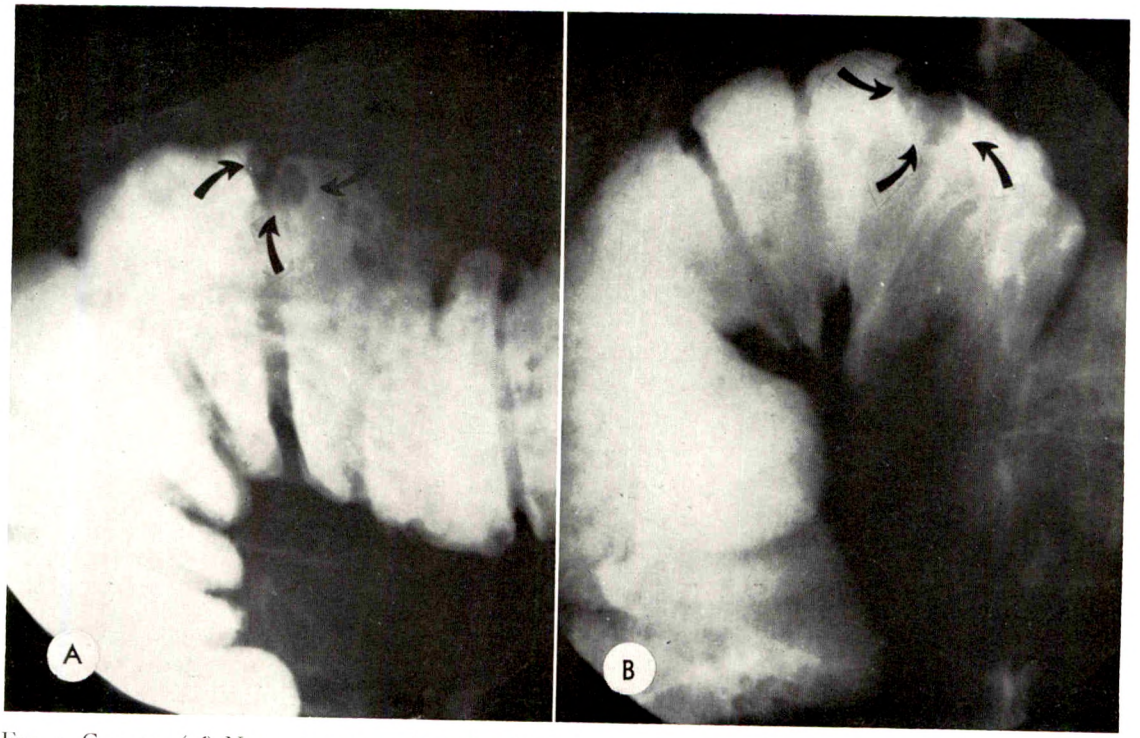


FIG. 9. Case IX. (*A*) Note 11 mm. sessile polypoid lesion at the apex of the hepatic flexure discovered on studies of November, 1956. (*B*) Study showing the increase in size of this polypoid lesion to 17 mm. in approximately 1 year of follow-up.

and, when encountered, should suggest the possibility of a malignant lesion. This case further proves that benign lesions may grow or show increase in size with the rate of growth not always predictable.

CASE IX (Fig. 9, *A* and *B*). A.S., a 50 year old white female, was admitted on October 21, 1957 for elective removal of a polyp of the hepatic flexure which had increased in size from 11 to 17 mm. on follow-up study of approximately 1 year. This patient had a gastrectomy in November, 1956 for a prepyloric gastric ulceration. At that time an 11 mm. polyp had beem demonstrated in the hepatic flexure of the colon on two separate studies. Since the surgeon felt that he could not treat both conditions at the same time, the polyp was left undisturbed.

Comment. This case illustrates a 1 year follow-up of a sessile, flat, polypoid lesion at the apex of the hepatic flexure which during this period increased in size from 11 to 17 mm. On this basis surgery was advised. Because of the location of the lesion, the surgeon chose to perform a right colectomy. The pathologist reported a benign adenomatous polyp.

ROENTGENOGRAPHIC FOLLOW-UP OF COLONIC POLYPS

In 1958 we expressed the opinion[7,8,9] that the smaller asymptomatic colonic polyp beyond the reach of the endoscope, especially in the older patient or in the surgical risk patient, should be managed conservatively and followed up by periodic roentgenographic studies. We felt that changes in size could be recorded with reliable accuracy with high kilovoltage compression techniques and that the necessity for surgery could be determined on the basis of change in size or growth (Cases I, II and III).

Collins, Loeffler and Tivey,[4] in 1956, studied the growth rates of human tumors and, based on the differential growth rates of metastatic pulmonary lesions originating from malignancies of the rectum and colon, determined doubling times of 49 and 123 days for such metastases. They concluded that when the growth of cancer is described

as a doubling process, the doubling time becomes a measure of the rate of growth. On the assumption of a constant rate of growth, an estimate of the total duration of a cancer could be made.

Their data are pertinent because they indicate that a growing tumor is likely to be malignant. Our follow-up studies confirm their findings in regard to the malignant polypoid lesion. In many of our cases in which colonic cancers developed from small polypoid lesions, we believe that there is a fairly accurate correlation of growth rate or "doubling time" as indicated in their studies. We have further noted that there is a differential growth rate between the benign and malignant polypoid lesion. Benign lesions will generally grow very slowly or not at all over prolonged observation periods.

Obviously, there are many unknown and unpredictable factors which affect the growth rates of colonic polyps and colonic cancers. To determine the exact duration of a cancer by means of the "doubling time principle" will not be possible in all cases; in fact, in some instances clinical material indicates that certain lesions are either of extremely low-grade malignancy or benign lesions which have undergone malignant degeneration. In such cases, the "doubling time principle" may be invalid except during the phase of active cancer growth.

We have had the opportunity to evaluate by roentgenographic methods approximately 300 cases with colonic polyps. The vast majority of these cases were detected by the use of high kilovoltage compression techniques. although in some instances retrospective analysis of earlier studies, double contrast studies or the expulsion studies, permitted a comparative evaluation. In 4 instances surgical removal was recommended on the basis of rapid growth rate during the first year of roentgenologic observation. In all benign adenomas were found. These are the only errors in our series of cases to date.

It is significant that the microscopic examination revealed the majority of larger colonic polyps (1 cm. or greater in size) to be benign. All of those polyps must have been very minute lesions at one time. Benign polyps may grow (Case VII) and show an increase in size on comparative roentgenographic studies. Once they have been discovered, their growth rate furnishes the best indication of their character.

We have accumulated a number of cases in which growth or increase in size of the polyp was reliably demonstrated by follow-up roentgenographic examinations. On subsequent removal and histologic study, the presence of benign adenomatous, papillomatous or adenopapillomatous polyps was established. In such cases, with a few exceptions, the increase in size was very slight and became manifest usually only after prolonged follow-up over a period of 2 or more years. One notable exception was a histologically proven benign adenoma recurring at the site of surgery in the sigmoid portion of the colon where a benign adenoma had been previously removed. This lesion was discovered 6 months after surgery on barium enema study and had tripled in size in approximately 1 year follow-up (Case VIII). Such a rapid growth rate suggested the possibility of a malignancy. In a second case of this type, a sessile polypoid lesion of the hepatic flexure increased from 11 to 17 mm. in 1 year. The colon containing this polyp was resected. The pathologist reported a benign adenomatous polyp (Case IX).

These observations indicate that any increase in size of a polyp within the first year should be regarded very suspiciously. A number of cases showing the development of frank colonic cancer from a 1 cm. polypoid lesion in all segments of the colon, usually within a 2 to 3 year period, were noted. Several examples in which longer periods of time were required for the development of malignancy have also been encountered; in one instance 12 years have elapsed before such a transformation. Hultborn[18] described a case requiring approxi-

mately 11 years for an obstructing carcinoma of the transverse colon to develop from a lesion measuring 3 to 4 cm. which presumably from its roentgenographic appearance was a villous tumor. We have observed the growth and development of the typical bulky polypoid or annular carcinoma in all colonic segments, confirming the findings of Hultborn,[18,19] Welin,[32] Epstein,[5] and others.

Thus, the rate of growth becomes the most important factor in determining the neoplastic potential of a colonic polyp under roentgenologic observation. The small malignant polyp or early carcinoma will show an increase in size early in the course of roentgenologic follow-up. Doubling in the volume of a polypoid tumor in 6 to 12 months or less indicates a high cancer potential. For this reason, any lesion showing an increase in size during the initial phases of follow-up should be surgically removed.

Slow growth occurring over extended observation periods is in favor of a benign polyp; however, sudden acceleration of growth or disproportionate increase in size at any stage of follow-up should suggest the possibility of malignant transformation or degeneration and, of course, is an indication for surgery.

Spratt and Ackerman[27] have applied the findings of Collins *et al.*,[4] and in 1960 recommended that lesions under 1.2 cm. in size be treated conservatively and observed for changes in size, properly assuming that an increase in size is the earliest indication of the presence of cancer. The basis for this recommendation was personal material which showed that the mortality attending the surgical removal of the colonic polyp exceeded the risk of the small polyps (1.2 cm. or less) being malignant.

PLAN OF FOLLOW-UP PROCEDURE

Our policy had been to recommend re-examination 3 months after discovery of a polypoid tumor 1 cm. or less in size, with subsequent re-examination at 6 months for 2 years. Provided no change had occurred, yearly examinations were then recommended.

Recently, in the light of our observations on the growth behavior of colonic carcinomas, these recommendations were modified in an effort to simplify the follow-up procedure. We have collected 15 cases roentgenographically documenting the growth of colonic carcinoma from polypoid tumors as small as 1 cm. in size. In all instances the time interval required for a 1 cm. polypoid tumor to develop into a frank colonic carcinoma varied between 2 to 3 years or longer (Cases IV, V, and VI). These observations indicate that colonic carcinoma grows quite slowly and further suggest that roentgenologic follow-up can be safely utilized as a means of determining whether a colonic polypoid tumor is benign or malignant; *e.g.*, the malignant polyp or early carcinoma will demonstrate growth (doubling in volume) in 6 to 12 months or less, whereas benign polyps will grow more slowly or may show no change on extended observation. Therefore we recommend follow-up study of patients with polypoid tumors 1 cm. or less in size in 6 months. If no growth occurs during this interval, a second examination is performed 6 months later. If no growth occurs during the initial year of study, this indicates the presence of a benign lesion; however, yearly follow-up examination is indicated. When polypoid tumors larger than 1 cm. are followed because the patient is elderly or medical complications are present and the surgical risk substantially greater, the initial progress study is carried out in 3 months.

RECOMMENDATIONS

Polypoid tumors larger than 1 cm. in size should be removed. However, in older patients, especially those with medical complications, larger lesions may be followed roentgenographically and the advisability of surgery determined on the basis of growth or absence of growth.

We feel it is probably safer to follow a

pedunculated polypoid lesion than a sessile lesion of comparable size since all authorities agree that there must be invasion of the stalk of a pedunculated polyp before metastasis can occur.

In cases being followed roentgenographically, the advisability of surgery in any given case can be determined on the basis of the following:

1. If a polyp increases in size during the first year of observation, surgical removal should be considered on the premise a growing lesion may be a malignant lesion.

2. The doubling in volume of a polyp in the first 6 to 12 months or less of observation indicates a malignant or potentially malignant lesion and the polypoid tumor should be removed.

3. Slow growth or no growth over observation periods of several years indicates a benign tumor.

Sudden acceleration of growth in such a polyp should suggest the possibility of malignant transformation and the tumor should be removed.

SUMMARY

A more conservative attitude for the management of colonic polyps beyond the reach of the endoscope is indicated especially in the older or surgical risk patient.

Autopsy studies have proven that 50 per cent or more of older patients have one or more colonic polyps, the vast majority being benign lesions. One cannot justify surgical removal of all polyps since theoretically surgery would be necessary in 1 out of every 2 patients over 60. The surgical risks would greatly exceed the risk of cancer.

Roentgenologic follow-up studies with high kilovoltage compression techniques have proven to be a simple, safe and highly accurate method for the determination of the cancer potential of the polypoid lesion.

Changes in size or growth, especially the rate of growth, will allow an accurate determination of the benignancy of polyps being observed. The advisability of surgery can be determined accordingly.

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PEDUNCULATED EPIDERMOID CARCINOMA OF THE MIDESOPHAGUS*

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THERE is a general belief that pedunculated polypoid lesions of the esophagus are benign.[1,3,8] Although uncommon, they are diagnosed on the barium studies of the esophagus without great difficulty. Malignant pedunculated lesions of the esophagus are extremely rare[4] and, due to the companion infiltration and rigidity of the esophageal wall, are easily confused with cardiospasm and stuck food particles.

It is further believed that malignant pedunculated esophageal lesions are sarcomatous[3] when located in the upper esophagus and adenocarcinomatous or carcinosarcomatous when located in the lower esophagus near the cardia.[4,6]

The case reported here demonstrates a different histologic type and unusual location of a pedunculated malignant polyp with rather typical roentgen appearance. To our knowledge, such a combination has not been reported. The awareness of the existence of pedunculated epidermoid carcinoma of the midesophagus could aid in suspecting similar lesions visualized on the barium swallow roentgenograms.

REPORT OF A CASE

A forty-eight year old white waitress was admitted to the hospital with the complaint of difficulty in swallowing solid food for the preceding five to six months, accompanied by a 25 pound weight loss. She used her finger for the purpose of dislodging the stuck food, after which she usually vomited blood. On the barium swallow study, the upper two-thirds of the esophagus was distended more than usual with the contrast material (Fig. 1 and 2). The lower part of this distended segment was rigid and barium remained there for a short time (Fig. 2 and 3). Once this rigidity eased, the lower esophagus appeared of normal caliber. There was a radiolucent filling defect in the midesophagus, very irregular in shape and giving the impression of accumulation of food particles (Fig. 1, 2 and 3).

A granular friable lesion was seen on esophagoscopy, extending from 20 to 30 cm. from the upper incisor teeth on the right side of the esophageal wall.

After a positive biopsy, the lesion was surgically resected and a peculiar pedunculated tumor was found (Fig. 4 and 5), approximately 5 cm. in length, with a pointed tip, very friable and yellowish-green in color. The base of the tumor was in continuity with the mucosa of the esophageal wall. Microscopically, the tumor was composed of irregular sheets of anaplastic squamous cells which extended to the muscularis. The tumor tapered proximally through the stalk to form a thin layer of anaplastic squamous cells infiltrating the epithelium of the esophageal wall. The final diagnosis was pedunculated epidermoid carcinoma.

DISCUSSION

Polypoid lesions of the esophagus can be sessile, but are more often pedunculated. The pedunculation is thought to be due to the suction or dragging action of the peristalsis.[3] Fibromas, papillomas, myxomas, myomas, lipomas and leiomyomas are the most common histologic types[1,2,3] and the usual location is in the upper esophagus. The polyps produce signs of obstruction and occasionally are regurgitated by the patient.[1] The roentgen findings are radiolucent filling defects with occasional demonstration of the stalk and without evidence of rigidity of the surrounding esophagus.

Very few isolated malignant polyps of the esophagus have been reported in the literature. Palmer[5] described a case of a polypoid, rather sessile type of squamous cell carcinoma of the lower esophagus. Piaget and Courderc[6] reported a pedunculated carcinosarcoma of the lower esophagus, and Feldman[4] stated that pedunculated polyps of

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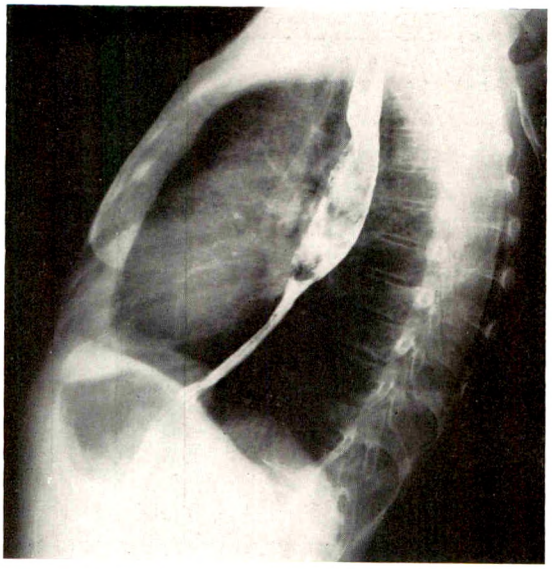


FIG. 1. Lateral roentgenogram of the chest taken during barium swallow. Note the distended upper two-thirds of the esophagus with a radiolucent defect in the midportion. The defect has the appearance of a foreign body.

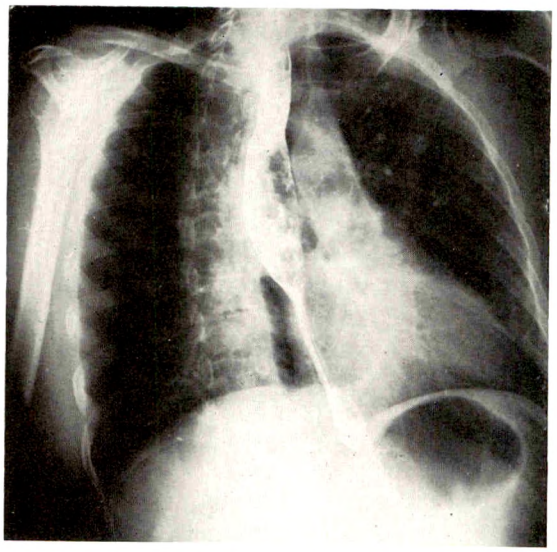


FIG. 2. Left anterior oblique roentgenogram taken during barium swallow showing same findings as in Figure 1. Note the normal lower esophagus.

malignant character are adenocarcinomas of the lower esophagus. The British authors[7] call the malignant polyps of the esophagus "papilliferous carcinoma." They state further that these tumors are friable on the surface and that the base of the tumor in the esophageal wall is indurated. Microscopically, the majority appears to be squamous cell type. No specific location of this malignant polyp is mentioned.

Roentgenologically, a malignant pedunculated lesion of the esophagus presents as a round or irregular filling defect in the lumen with definite alteration of the peristaltic movements and of the elasticity of the esophagus.[3] These findings could be confused with cardiospasm[1] or food stagnation in the esophagus. The awareness that such



FIG. 3. Spot roentgenogram of the midesophagus taken during barium swallow. The tumor is well outlined as a radiolucent filling defect, occupying the entire lumen. The rigidity of the esophageal wall, infiltrated by neoplastic cells, temporarily retains barium immediately below the tumor (arrow).

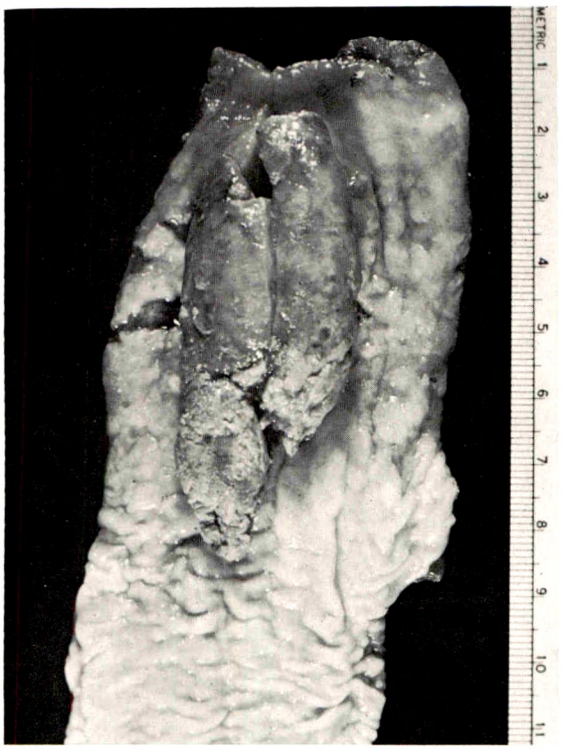


FIG. 4. Photograph of the surgical specimen showing the tumor mass on the lateral wall of the esophagus.

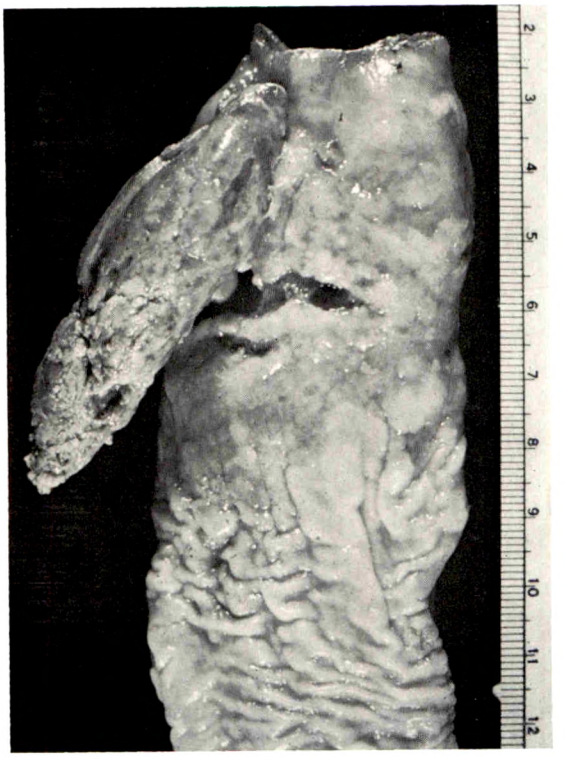


FIG. 5. Photograph of the same specimen as in Figure 4. Note the typical appearance of a pedunculated polyp. The surrounding mucosa has lost its normal pattern. Microscopically, the epithelium of the esophageal wall was infiltrated by anaplastic squamous cells. The polyp is an epidermoid carcinoma.

malignant polyps can exist in the midesophagus will help in making the diagnosis earlier.

SUMMARY

A rare pedunculated epidermoid carcinoma of the midesophagus is reported. Usually esophageal polyps are benign and malignant polyps are most often located in the upper or lower esophagus. The roentgen signs are briefly discussed.

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FUNCTIONAL ESOPHAGEAL OBSTRUCTION DUE TO LEUKEMIC INFILTRATION*

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INVOLVEMENT of the gastrointestinal tract by myelogenous leukemia is relatively rare,[2,5,11] and infiltration of the esophagus, occasionally noted with lymphomas, is rarer still.[2,6,9] We have recently encountered a case of acute myelogenous leukemia, in which complete functional obstruction was associated with localized infiltration of the esophagus. Since this lesion, to our knowledge, has never been observed as a cause of esophageal obstruction, we are reporting our case as the first with these unique findings.

REPORT OF A CASE

S.W. (COH 60–913), a fifty-eight year old white male, was admitted to the hospital with anorexia and weakness which was progressive over a six month period. Intermittent dysphagia was also noted during this time. Three months prior to admission, the patient was found to be severely anemic. A bone marrow biopsy was reported as showing leukemia. Dexamethasone therapy was started, 10 mg. daily, but proved to be ineffective. A barium swallow study showed no abnormalities of the esophagus two months prior to admission.

There was a history of two serious episodes of rectal bleeding within the preceding three years. In both instances, abdominal exploration was carried out. A large leiomyosarcoma was removed from the terminal ileum at the time of the first surgery, and a subtotal gastric resection was performed at the second operation. On both occasions, bleeding was thought to be due to a duodenal ulcer. The esophagus was normal on roentgen studies during this period.

At physical examination, the patient appeared wasted and chronically ill. Small lymph nodes were palpable in both axillae. No abdominal organs or masses were noted. The remainder of the physical examination was not remarkable.

Initial laboratory data were as follows: hematocrit 33 per cent; white blood cell count 3,000, with 4 per cent segm., 1 per cent band, 81 per cent lymphocytes, 1 per cent prolymphocytes, 2 per cent eosinophils and 11 per cent blasts; platelet count 300,000. A bone marrow examination on admission was consistent with acute myelogenous leukemia (Fig. 1).

On the first hospital day, the patient developed a temperature elevation to 39° C. and a pleural friction rub over the left chest. The following day painless swelling appeared of the entire left leg, and this combination of findings was interpreted as phlebothrombosis of the deep leg veins with pulmonary embolism. Anticoagulant therapy was begun. A barium swallow examination showed complete obstruction to the passage of barium in the middle third of the esophagus at fluoroscopy (Fig. 2). The febrile course continued, and despite large doses of corticosteroids and antibiotics, the patient expired on the fifteenth hospital day.

At autopsy, multiple bilateral pulmonary infarctions were found. There was no evidence of recurrence of the abdominal leiomyosarcoma. Lymphadenopathy was minimal, with the largest lymph nodes in the mediastinal area measuring 1.5 cm. The liver was grossly normal, and the spleen was atrophic, weighing 20 gm. There was widening of the middle and lower thirds of the esophagus with thickening of the walls (Fig. 3). Microscopic evidence of leukemia at the time of autopsy was confined to scattered areas of the bone marrow and the walls of the esophagus (Fig. 4). In addition, the esophagus in this area was infiltrated with *Candida albicans* (Fig. 5).

DISCUSSION

Infiltration of the gastrointestinal tract by leukemic cells producing localized tumors is not unusual according to many authors[10,11,12] who have reported their findings in the esophagus, stomach and intes-

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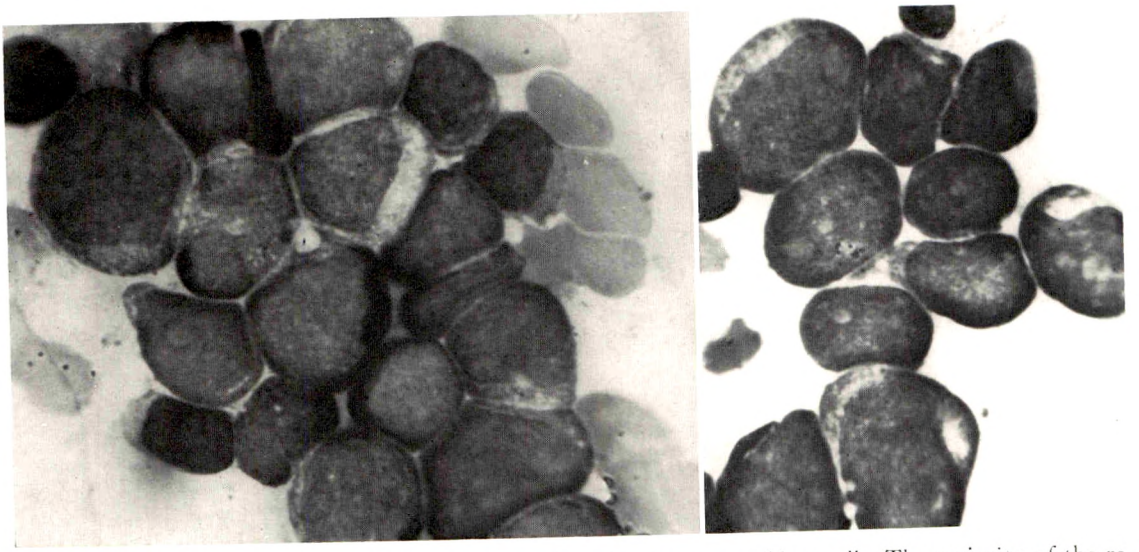


Fig. 1. Hypercellular bone marrow showing approximately 50 per cent blast cells. The majority of the remaining cells are progranulocytes. A few myelocytes and more mature forms of the granulocytic series are also present.

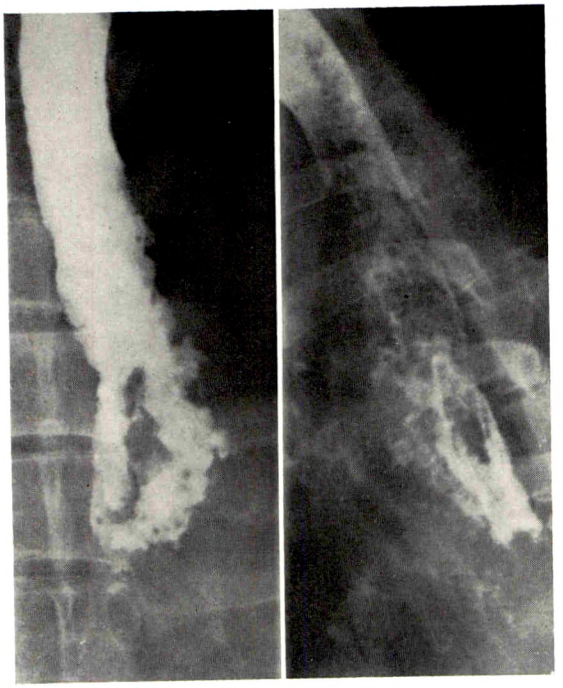


Fig. 2. Barium swallow study shows dilatation with a shaggy irregular mucosal pattern and complete obstruction beyond the junction of the middle and lower thirds of the esophagus.



Fig. 3. Gross specimen of the esophagus showing serpiginous grayish elevations interspersed with ulcerated areas in the dilated junction of the middle and lower thirds and return to normal 4 cm. above the cardia.

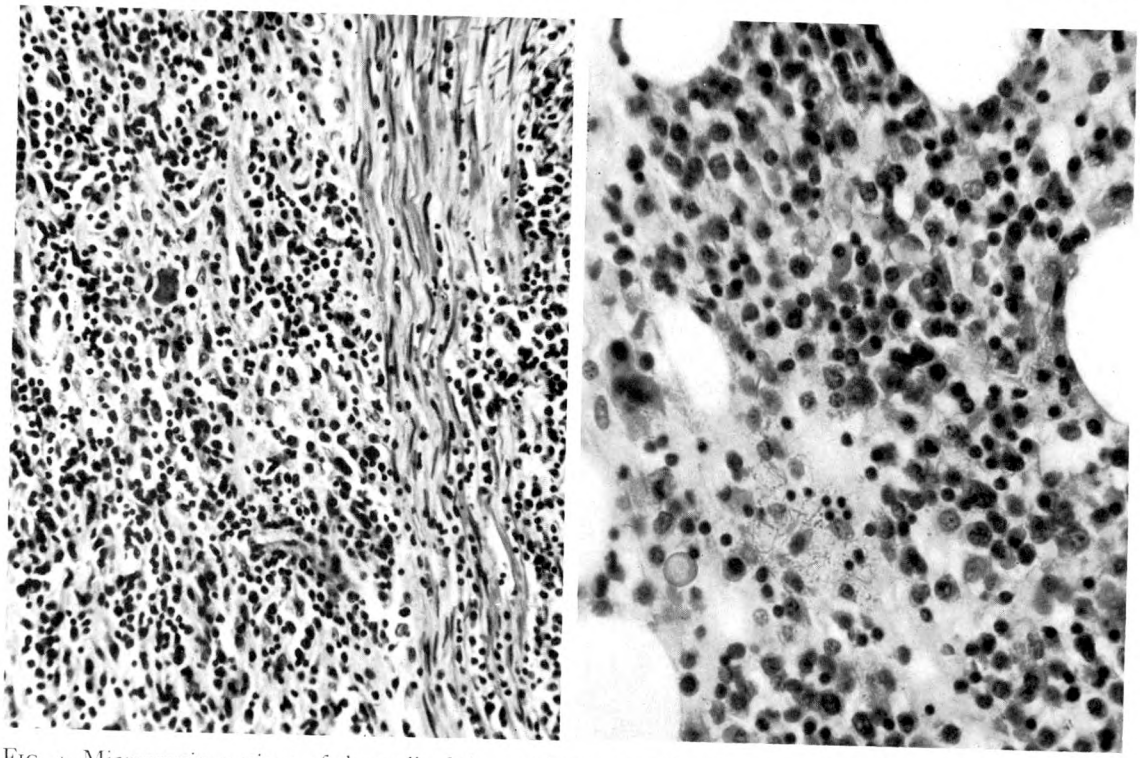


FIG. 4. Microscopic sections of the wall of the esophagus reveal replacement by cellular infiltrate of blast cells, promyelocytes and some myelocytic forms closely resembling those found in the autopsy bone marrow specimen.



FIG. 5. Hyphae and budding forms of *Candida albicans* in the necrotic tissue and exudate in the esophagus.

tines in chronic lymphatic leukemia cases. Boikan,[2] Pearson *et al.*,[11] and Wintrobe[14] have asserted that involvement of the gastrointestinal tract in myelogenous leukemia is very rare. Also, intestinal tract involvement in the acute leukemias is found less frequently than in chronic lymphatic leukemia.[15] The rarity of esophageal infiltration is further emphasized by the fact that standard medical and surgical texts[1,3,7,13] on the gastrointestinal tract do not mention it. Dameshek and Gunz[4] state that the esophagus is rarely inolved.

Kirschbaum and Preuss[9] reported on 123 autopsied leukemic cases, of which 75 were designated acute. Seventeen of the total group showed "leukemic infiltration of the intestines," but the esophagus was not specifically mentioned, and dysphagia was not noted.

Gunz and Hough[6] noted occasional esophageal infiltrates in 97 cases of acute leukemia in patients over the age of fifty. An interesting observation of these authors was the great variety of organ involvement noted at autopsy, often bearing little relationship to the severity of the clinical status.

We had considered several possibilities to account for the unusual findings on the barium swallow study of our patient. The appearance of the dilated segment of the esophagus suggested an esophageal carcinoma or lymphosarcoma with extension upward from the obstructing lesion, or retained food particles associated with an obstructing lesion of the esophagus. The history of a previously resected leiomyosarcoma also brought up the consideration of a metastatic process producing the changes in the esophagus.

At autopsy, barium was still present at the level of the obstruction, several days after the examination. Leukemic cells infiltrated the full thickness of the esophageal wall in the middle third, and large numbers of Monilia organisms were also found in this segment.

Recently, Kaufman *et al.*[8] described irritability and spasm of the esophagus involved by moniliasis. They point out the frequent occurrence of this lesion in blood dyscrasias and stress the shaggy, irregular appearance of the involved mucosa. However, in none of their cases was complete obstruction noted despite the presence of narrowing and rigidity of the esophageal lumen. In our case, there was complete obstruction to the passage of barium, associated with marked dilatation of the involved segment. All layers of the esophagus were replaced by leukemic infiltration. The type and the distribution of the cells in the leukocytic infiltration clearly indicated that this was not a response to the monilial infection. We consider, therefore, that the monilial infection was an incidental finding, and that the functional obstruction of the esophagus was due to destruction of the muscular wall and its innervation by the leukemic infiltration.

It is of interest that treated leukemia may be modified so that infiltration in the usual sites is no longer present. As an example, the spleen in our patient was actually atrophic, weighing only 20 gm. and showing no evidence of leukemia microscopically.

Although clinically our patient presented no diagnostic problem with regard to the underlying disease, the situation from the point of view of anatomic pathology was more perplexing. The clinical diagnosis of leukemia was made certain by the findings of 50 per cent blast cells within the bone marrow. On the other hand, at the time of death, there was no purpura, lymphadenopathy, splenic atrophy, or leukemic infiltration of liver or kidneys, and only a moderate hyperplasia and immaturity of bone marrow. The leukemic infiltration in the wall of the esophagus, complicated as it was by the necrosis and monilial growth, produced the unusual fluoroscopic appearance and presented the only extensive leukemic infiltration. Actually, from its cellular nature, it aided and confirmed the diagnosis of the leukemia.

SUMMARY

A patient with a functional obstruction of the esophagus due to localized infiltration by acute granulocytic leukemia is presented with a review of the pertinent literature.

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VOL. 88, NO. 4

ACHALASIA OF THE ESOPHAGUS IN A DACHSHUND*

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CARDIOSPASM, also known as achalasia or megaesophagus, is essentially a perversion of the physiology of the lower esophagus. Following deglutition there is failure of peristalsis and failure of relaxation of the lower esophageal complex. Under the influence of retained food and secretions, the esophagus slowly dilates and may reach giant proportions.

The condition apparently results from a postganglionic cholinergic denervation of the esophagus possibly caused by some unknown form of injury. This conclusion[1] is predicated on the abnormal histologic appearance of the myenteric plexus of Auerbach and on pharmacologic evidence resulting from the "mecholyl effect," which is a hypersensitive response of denervated tissue to a neurohumoral agent.

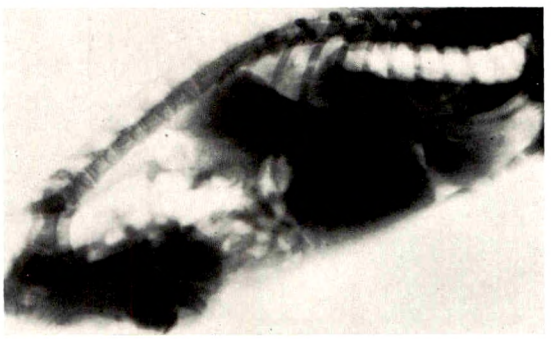


FIG. 1. Achalasia in a dachshund as seen in the normal walking posture.



FIG. 2. Achalasia in the upright posture.

Recently a greater incidence of cardiospasm has become apparent. Swenson and Oeconomopoulos[3] described the condition in 6 children ranging from two and one-half to twelve years of age. Patterson[2] reported a case of cardiospasm in a Chihuahua dog and stated that this condition is as common in dogs as in man and that its appearance seems to be identical in the two species. He did not encounter the condition in cats, horses nor cows.

We examined a young dachshund which was unable to retain food. A barium suspension examination revealed a tremendous dilatation of the esophagus. Roentgenograms taken in the normal walking (Fig. 1) and upright (Fig. 2) postures showed fluid levels in the widened esophagus with absence of peristalsis. The lower end of the esophagus had a cone-like outline with smooth borders and permitted only a trickle of barium to reach the stomach.

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VOL. 88, NO. 4

ROENTGENOLOGIC FEATURES OF CONGENITAL BILATERAL ANTERIOR DIAPHRAGMATIC EVENTRATION*

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NEW YORK, NEW YORK

THE roentgenologic diagnostic aspects of unilateral diaphragmatic eventration and diaphragmatic herniation have been amply described;[2–16,19–26] however, with the exception of one questionable case,[27] the author has been unable to find a report of bilateral partial congenital eventration of the diaphragm. It was therefore felt that the presentation of the case histories of 2 infants who were extensively studied because of the unusual appearance of the mediastinal silhouette and a discussion of this abnormality would prove of interest.

REPORT OF CASES

CASE 1. G.R., a white male, was admitted to the Bronx Municipal Hospital Center on January 9, 1961, at the age of 5 days because of respiratory distress. The patient was born spontaneously to a 28 year old P_4 G_4 serology negative female, following an uneventful pregnancy of $8\frac{1}{2}$ months' duration. The birth weight was 5 pounds, 12 ounces. At birth the patient was covered with meconium and was cyanotic and had respiratory distress. The placenta was noted to have multiple infarctions. The patient was begun on chloromycetin therapy. The respiratory distress improved only slightly in oxygen. At 4 days of age he developed watery stools and was transferred to the Bronx Municipal Hospital Center the next morning.

Family History. There are 3 siblings ages 8, 6 and 4 who are well. There is no history of congenital anomalies.

Physical Examination. Temperature 99, pulse 140, respiratory rate 80, head circumference 30.5 cm., length 22.5 cm., weight 2,500 gm.

The infant was dusky out of oxygen and had mild respiratory distress without costal retraction. Potter's facies with a receding jaw, large low-set ears and a beaked nose were noted. The head appeared small with the sutures and fontanels normally opened. There was a cleft palate and a web neck. Decreased breath sounds were present in the left hemithorax but no rales were heard. The heart was normal. Weak femoral pulses were found. Neurologic examination revealed a poor Moro reflex with a weak cry; no grasp, but good muscle tone was present.

Laboratory Data. Urinalysis: albumin 1 to 2, red blood cells 5 to 8 and white blood cells 10 to 15 per high power field. Blood studies: hematocrit 85 per cent, white blood cell count and differential were not remarkable. A roentgenogram of the chest taken on admission showed a mediastinal silhouette which was apparently enlarged to the right and to the left. In the lateral projection a mass appeared to be continuous with the anterior portion of the diaphragm. A suggestion was made that this represented an anterior mediastinal tumor. On further evaluation the next day, a bilateral diaphragmatic eventration was suspected, and a bolus of approximately 30 cc. of air was introduced by hypodermic needle into the abdominal cavity. Upright anteroposterior and lateral roentgenograms of the abdomen and chest were taken and demonstrated a bilateral diaphragmatic eventration continuous over the midline.

An intravenous pyelogram showed adequate kidney function and morphology on the left side but the right kidney was not visualized. Roentgenograms of the skull failed to show calcifications. The patient's course appeared stabilized in time and the hematocrit finally decreased to about 35 per cent. Approximately 6 weeks after admission he was found dead.

Autopsy Report. 1. Potter's facies. 2. Uremia (clinical): (a) multicystic right kidney; (b) stenosis of the right ureter at the ureteral pelvic junction; (c) absence of the right renal artery; and (d) pyelonephritic scars right kidney. 3. Coarctation of the aorta, infantile type: (a) patent ductus arteriosus; (b) hypoplastic left ventri-

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cle; (c) dilatation of the ascending aorta; (d) hypertrophy of the left ventricle; and (e) endocardial thickening of the left outflow tract. 4. Cleft palate: (a) hemorrhagic bilateral pneumonia. 5. Bilateral diaphragmatic eventration: (a) lobular liver. 6. Polylobulation of lung. 7. Early closure of small fontanel. 8. Web neck. 9. Accessory spleen.

After the microscopic examination of the brain, the final pathologic diagnosis included cerebral toxoplasmosis.

Case II. J.M., a 10 month old male, was admitted to the out patient department for neurologic evaluation. On anteroposterior roentgenograms of the dorsal spine, it was noted that he had an anterior mediastinal mass which contributed to an extremely unusual cardiac silhouette. His physical examination and laboratory work-up were essentially normal. The rest of this patient's hospital stay was predominantly concerned with locating the correct cause for the unusual cardiac and mediastinal silhouette. Fluoroscopic examination of the chest failed to show distinctive cardiac pulsations and it was considered possible that multiple pericardial cysts contributed to the unusual appearance of the mediastinum. In retrospect, the apparent lack of adequate pulsation of the heart was probably due to its abnormal location in relation to the anterior inferior mediastinal mass. The thymus decreased in size after approximately 5 days of corticoid treatment (Fig. 8). This removed the possibility that the mediastinal silhouette was due to thymic enlargement. An angiocardiogram showed an uplifted, elevated heart in relation to the mass which was lying inferiorly and anteriorly. A small aortic coarctation was also seen. It then became apparent that we were dealing with a mass which seemed to be separated from the cardiac structures, but which occupied both right and left paracardiac spaces. Thirty cubic centimeters of air were instilled into the peritoneal cavity by hypodermic syringe and upright and lateral roentgenograms demonstrated conclusively that the mass was indeed an anteriorly located, bilaterally eventrated diaphragm, with herniation of the liver into the general area of the thorax. The liver conformed to the diaphragmatic contour.

A barium enema study was done subsequently and showed elevation of the transverse colon.

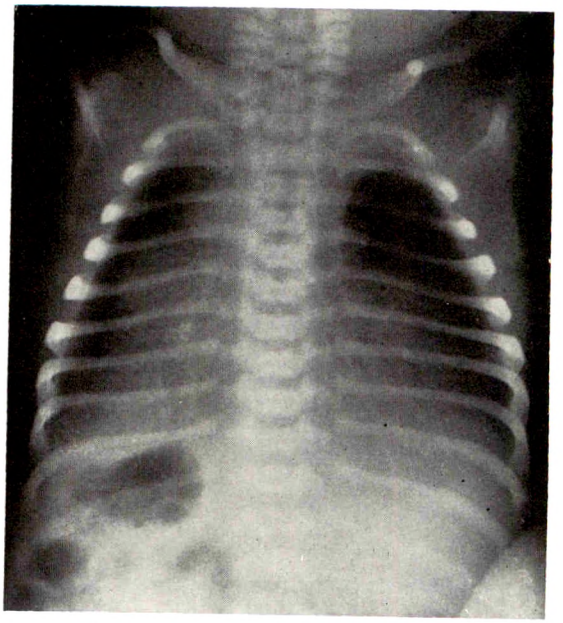


Fig. 1. Case 1. A posteroanterior roentgenogram of the chest on admission shows the lack of a typical diaphragmatic contour both to the right and to the left of the mid-line. It is also very difficult to determine the actual cardiac contour.

ROENTGENOGRAPHIC FINDINGS

Careful study of the routine roentgenograms of the chest of both of these patients revealed the rather typical bell-shaped appearance of an anterior, bilateral partial diaphragmatic eventration (Fig. 1 and 5). Consistent with Felson's silhouette sign, there was an apparent absence of the anterior aspects of both hemidiaphragms in the lateral projection. In Case 1, particularly, the normal contour of the heart was obliterated, suggesting, at first glance, a tumor of the anterior mediastinum (Fig. 2 and 6). Also, on the lateral projections, the diminutive appearance of the abdominal portion of the liver indicated that a large portion of the liver was elevated, conforming to each dome of the diaphragm.

It was only on the posteroanterior roentgenogram of the chest that the unusual appearance of the mediastinal sihouette was seen. In both cases the mediastinal silhouette was enlarged to the right and to the left of the midline in a somewhat bell-shaped pattern. It is interesting that, in

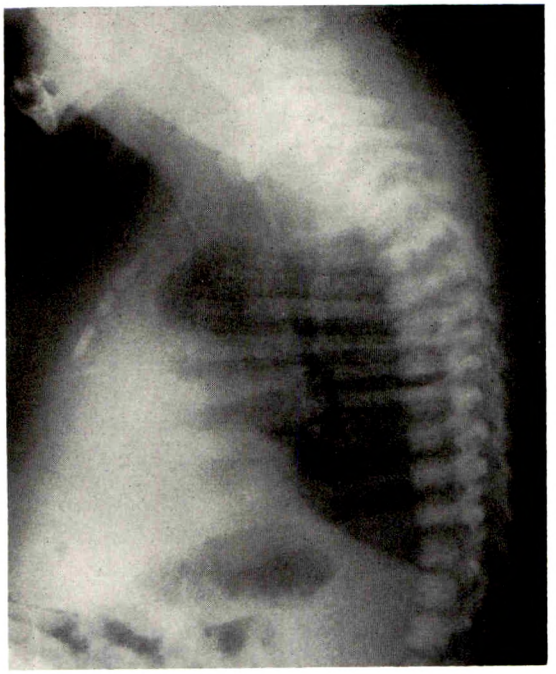


Fig. 2. Case I. A lateral roentgenogram shows complete obliteration of the anterior portion of the diaphragmatic contour. Note the apparent lobular nature of the anterior mediastinal mass and the diminutive appearance of the liver in the abdominal cavity.

Case II, the first impression was to rule out diaphragmatic eventration (Fig. 7, *A–C*) and to consider the presence of multiple pericardial cysts; however, an angiocardiogram demonstrated a normal heart with a small coarctation. Of important significance was the elevation of the heart with its somewhat peculiar rotation caused by the diaphragmatic eventration (Fig. 9, *A* and *B*).

If one has a high enough level of suspicion after seeing the unusual silhouette on the posteroanterior and lateral roentgenograms of the chest, instillation of a small quantity of air, or other less potentially dangerous gas such as CO_2 or N_2O, into the abdominal cavity can be readily accomplished without any physical disability to the patient.[4,17] Upright and lateral projections of the abdomen at this time will show the characteristic appearance of air under the eventrated portions of the diaphragm and actually the associated por-

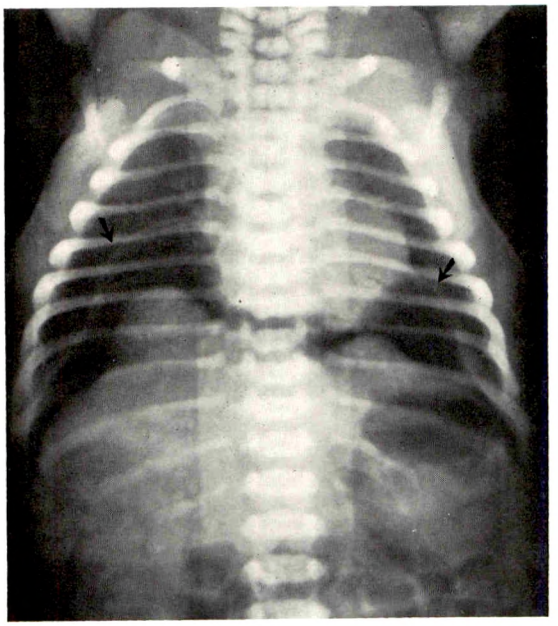


Fig. 3. Case I. An upright posteroanterior roentgenogram of the chest after the instillation of air into the abdominal cavity demonstrates the air under the eventrated portion of the diaphragm and shows the rounded liver nodules which follow the contour of the eventrated diaphragm.

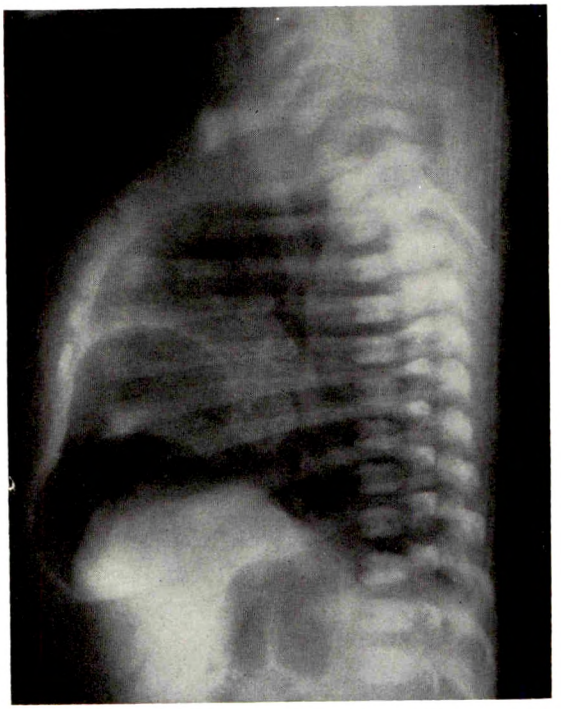


Fig. 4. Case I. A lateral roentgenogram shows to better advantage the loculation of the air in the eventrated portion of the diaphragm anteriorly.

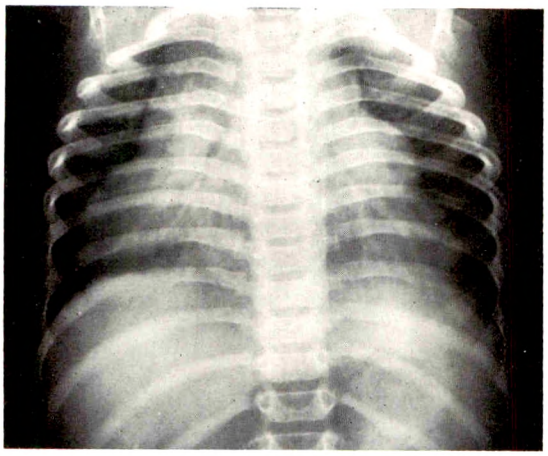


Fig. 5. Case 11. A posteroanterior roentgenogram of the chest shows the loculated contour of the mediastinal silhouette. It is impossible to see the outline of the heart.

tions of the liver will be outlined (Fig. 3, 4, 11 and 12).

DISCUSSION

It is important, but difficult sometimes, to differentiate between partial diaphragmatic eventration and diaphragmatic herniation. In the latter, a portion of the abdominal contents almost always protrudes into the chest. There is usually a peritoneal sac covering the portion of herniated abdominal contents. There are in the diaphragm several areas of potential congenital deficiency and other points of potential weakness, and these are the usual sites of both the congenital and acquired hernias. In the discussions of diaphragmatic hernia, anterior herniations through the foramen of Morgagni are described, and are usually said to appear in the right paracardiac region and only rarely through the analogous costosternal foramen on the left, due presumably to the presence of the heart. A right-sided hernia through the foramen of Morgagni may produce characteristic displacement of certain abdominal organs. When it contains only omentum, a shadow of soft tissue or water density is seen lying anteriorly next to the cardiac margin. In some cases colon, small bowel, or rarely the stomach may be present within the herniation sac and the appearance of the air in the structure may help in identification. Also, an inverted, V-shaped upward displacement of the colon may indicate potential herniation of abdominal structures towards the area of suspicion (Fig. 10). As opposed to the very rare recorded instances of bilateral anterior herniation, there are numerous reports of bilateral herniation through the foramina of Bochdalek, or the posterior lumbocostal triangle, situated in the posterior aspect of each hemidiaphragm.

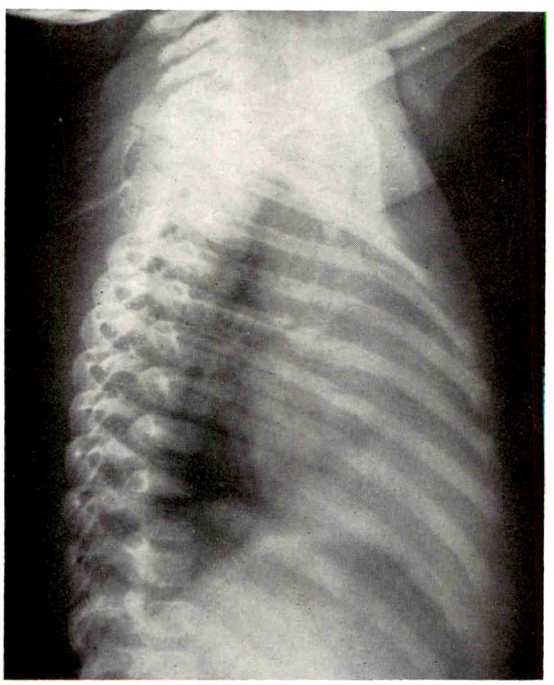


Fig. 6. Case 11. A lateral roentgenogram shows the prominent thymus and the apparent obliteration of the anterior half of both hemidiaphragms.

Diaphragmatic eventration, on the other hand, is usually considered to be due to the weakness of the muscular diaphragm and is often associated with trauma. Reed and Borden[21] present an excellent review of the historical aspects of bilateral total diaphragmatic eventration, tracing the first anterior description back to the mid-eighteenth century.

In a sense when one deals with a congenital defect, there is only a semantic differentiation between the appearance of an anterior abnormality due to a diaphragmatic eventration as compared to that due to a diaphragmatic hernia. In a review of

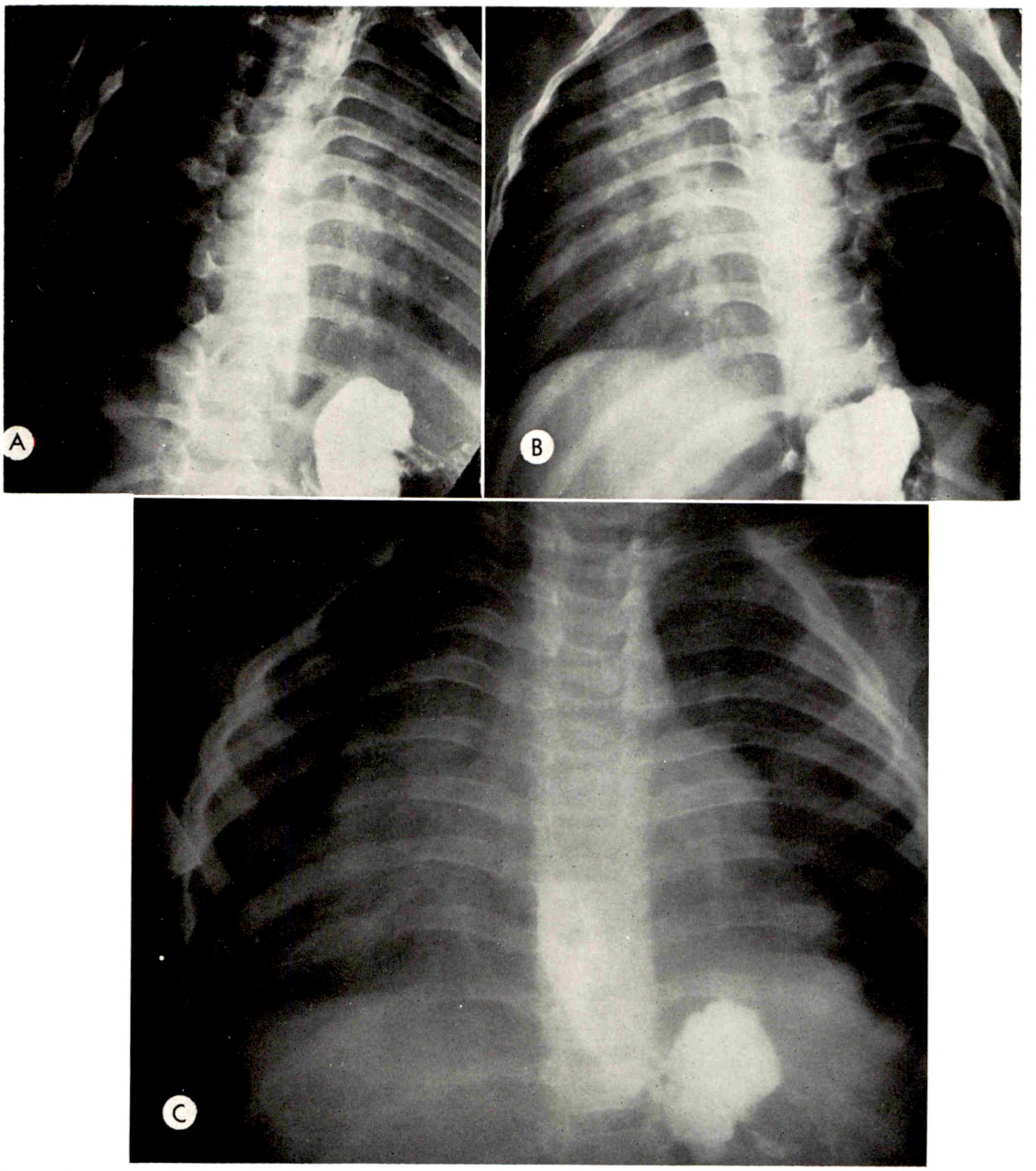


Fig. 7. Case 11. (*A* and *B*) Oblique roentgenograms of the thorax show apparent intact nature of both hemidiaphragms. (*C*) An anteroposterior roentgenogram of the chest using barium also gives the impression that the diaphragms are intact bilaterally. Because of this it was felt that diaphragmatic eventration was unlikely.

the embryology of the diaphragm by Wells[27] in 1954 the only description of a bilateral diaphragmatic abnormality is presented which could be accepted as that of a bilateral diaphragmatic eventration. Wells, himself, described this as a bilateral hernia. Ravitch and Handelsman[20] in their clinical evaluation do not distinguish between anterior hernia and anterior eventration. Wells studied 4 autopsy cases of diaphragmatic hernia, 3 in infants. His Case 4, that of a premature female weighing 1,730 gm.,

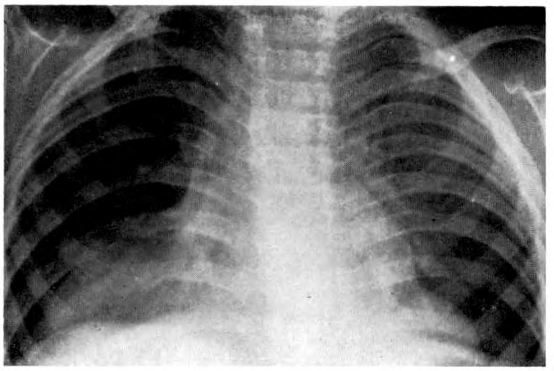


Fig. 8. Case II. After 5 days on meticorten a decrease in the size of the thymus was noted.

showed what he considered to be an early stage of bilateral hernia in the ventrolateral portions of the sternocostal triangles, corresponding to the foramen of Morgagni. These were described as being abnormally large. He considered this to be due to a congenital defect in the muscular layer of the diaphragm, but analogous to the esophageal hiatus hernia, where a serous sac is always present. Wells describes a bilateral V-shaped gap in the muscle of the anterior costal part of the diaphragm extending



Fig. 10. Case II. A barium enema study shows some elevation of the transverse colon suggesting elevation of the abdominal organs towards the thorax. This should have been an indication that the defect in the diaphragm included the liver.

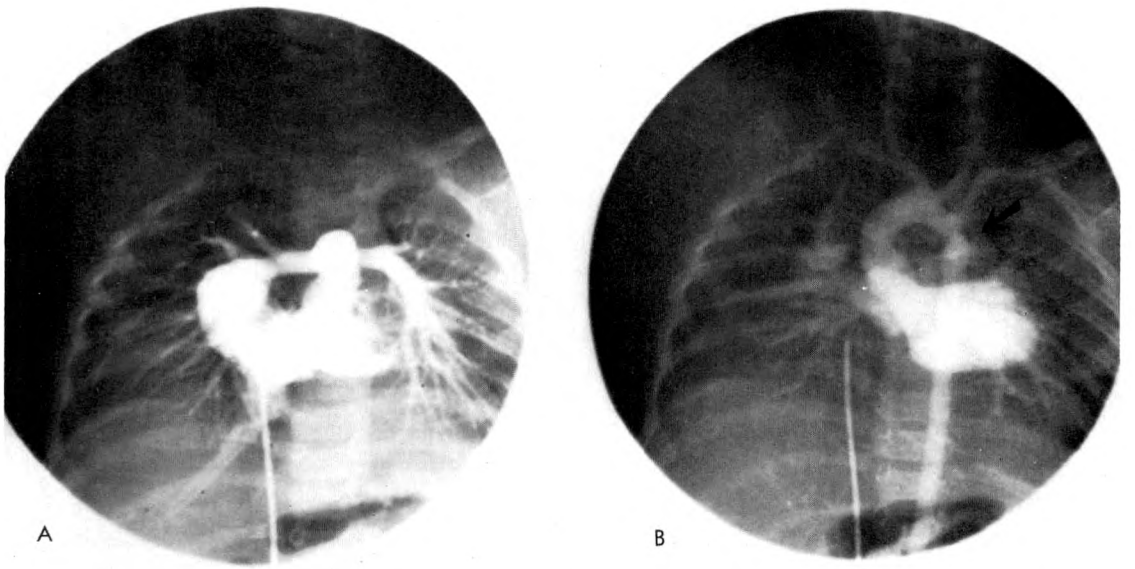


Fig. 9. Case II. (*A*) Levo- and (*B*) dextro-cardiograms demonstrate the elevated position of the heart in relation to the diaphragm. Coarctation of the aorta is also evident.

from the sternum medially to the eighth rib laterally. The dimensions of the right gap were approximately 24 by 22 mm. and of the left gap 25 by 16 mm. The hernial sacs he described therefore were composed of two layers, peritoneum and pleura. The depth of the right sac was 10 mm. and was greater than that of the left which was 5 mm. Each sac was occupied by an abnormal nodule of the liver. It appeared to Wells that the area of muscle which was deficient in the anterior part of the diaphragm left only the pleural and the peritoneal surface of the diaphragm as supporting structures. It is interesting to compare the findings of this patient with those of Case 1 of our series as described in the autopsy protocol. "A bilateral defect in the muscular portion of the diaphragm is noted with replacement of about 6 cm. of the anterior portion of the diaphragm by a thin fibrous transparent membrane. On the right side this membrane has been pushed up to the level of the 5th rib by a portion of the right lobe of the liver. On the left side the dome extends up to the 6th rib. There is no herniation of abdominal viscera into the thoracic cavity."

It is obvious that there was a virtual elimination of the muscular portion of the diaphragm anteriorly, and because of this weakening of the diaphragmatic structure, an eventration of the diaphragm developed.

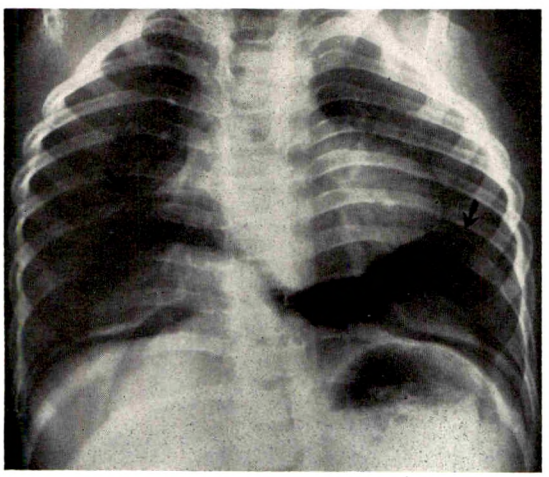


Fig. 11. Case II. Air instillation into the abdominal cavity shows the characteristic appearance of air under the eventrated portions of the diaphragm.

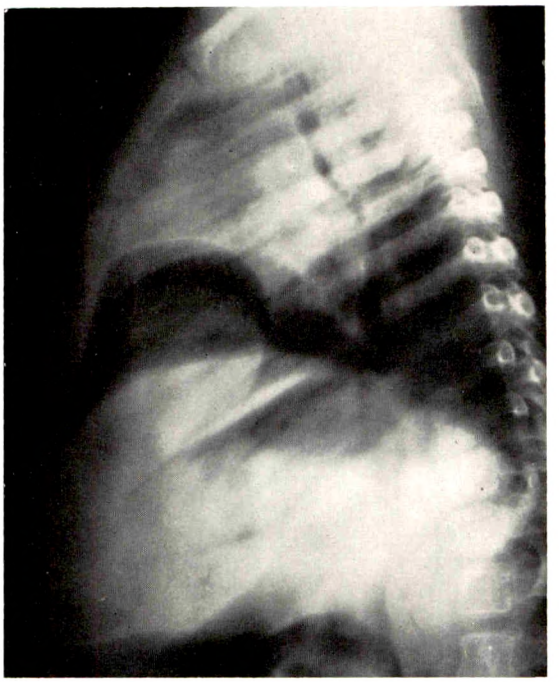


Fig. 12. Case II. An upright lateral roentgenogram of the chest after the introduction of air into the abdominal cavity shows the characteristic appearance of eventration of the diaphragm.

That the liver conformed to the weakness in the diaphragm indicates that this process probably took place relatively early during the embryologic development of the fetus. Bremer[3] suggests that accompanying general disease (*e.g.*, anemia) may be a contributing factor in causing degeneration of the binding structures of the muscular portion of the diaphragm, thereby allowing it to be more readily torn or weakened. There is no conclusive evidence for this.

CLINICAL CONSIDERATIONS

In the first case considerable discussion ensued regarding the possibilities of surgical repair of the bilateral eventration. It was difficult to understand why the patient had an elevated hematocrit and whether this could be secondary to respiratory embarrassment. The child's respiratory problem gradually improved and did not necessitate surgical repair.

In Case II it should be noted that the child was, and still is, completely asymptomatic and one must presume that at the

present time, at least, no surgical intervention is indicated.

SUMMARY

1. Two cases of bilateral congenital diaphragmatic eventration are presented.

2. A characteristic appearance of an enlarged and deformed mediastinal silhouette was noted and is commented upon.

3. Use of intraperitoneal gas insufflation is suggested as a conclusive diagnostic procedure.

4. The patients presented are compared with a case described in the embryologic literature.

5. A note is made as to the clinical handling of these patients.

6. Association of these congenital abnormalities with others, such as coarctation of the aorta, shows agreement with many authors who feel that congenital anomalies are not usually isolated.

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HEMANGIOMA OF THE LIVER WITH THROMBOCYTOPENIA*

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THROMBOCYTOPENIA occurring with benign hemangioma of the skin in infants and children has been well established. The available evidence supports the theory of the destruction of platelets within the tumor. This report concerns the finding of thrombocytopenia in a patient with a large hemangioma of the left lobe of the liver.

REVIEW OF THE LITERATURE

Shumacker[19] reviewed the literature on hemangiomas of the liver in 1942. He found 66 cases reported and added one of his own. Thrombocytopenia was not reported in any of these, although there was little mention of the hematologic values in any of the cases. The symptoms usually described were vague gastrointestinal complaints, such as bloating, nausea, anorexia, and dyspepsia. The outstanding finding on physical examination was the presence of a mass (in 54 of 67). Females predominated by a ratio of 4.5:1. A correct preoperative diagnosis was made in only 2 cases. In one, the abdominal mass was unusually compressible, and in the other, a bruit was heard over the tumor. Shumacker recommended surgical removal as the treatment of choice for hemangioma of the liver, and indicated that the greatest danger associated with such tumors was spontaneous rupture.

There have been numerous reports of hemangioma of the liver since this classic study. Hemangiomas are more frequently found in the liver than any internal organ,[22] and are noted in from 2 to 7 per cent of all autopsy specimens.[4,15] The great majority of these tumors are small, produce no symptoms, and are found incidentally at autopsy or laparotomy. Only the large tumors produce symptoms.

Kasabach and Merritt[11] reported the first case of hemangioma of the skin with associated thrombocytopenia in 1940. A few other cases were reported later, but there remained considerable doubt as to whether these two conditions were actually related or occurred merely by chance. Approximately 25 cases are reported in the English literature. It is now clearly established that the thrombocytopenia is secondary to the hemangioma. Good *et al.*[7] believe this to be the result of sequestration, utilization, and destruction of platelets within the hemangioma. Platelet thrombi have been found within the hemangioma producing vascular occlusion. Gilon *et al.*[6] reported simultaneous platelet counts from the tumor and the peripheral blood of their patient, and demonstrated a significantly higher concentration of platelets in the tumor vessels.

To date, the reported cases of thrombocytopenia and hemangiomas have been in infants and young children. The only patient over 3 years of age was a girl of 13.[6] The thrombocytopenia disappears when there is regression of the tumor, whether this be spontaneous or as a result of therapy.

Treatment of the vascular tumors of the skin has varied considerably. Splenectomy, surgical excision, blood transfusions, steroids, and irradiation have all been used, with varied results. Spontaneous regression of the hemangioma has been reported.[23]

REPORT OF A CASE

M.T., a 32 year old white female, was first ad-

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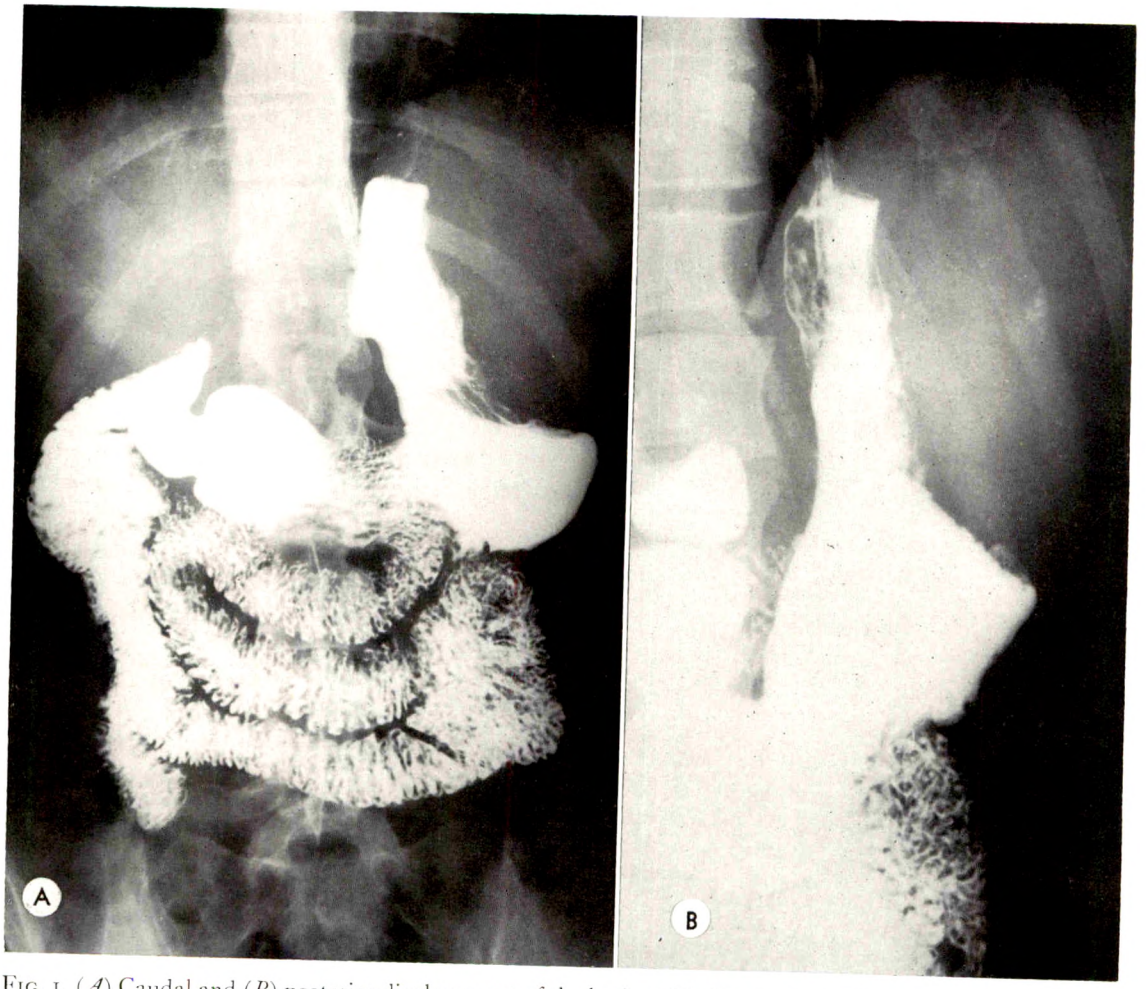


FIG. 1. (*A*) Caudal and (*B*) posterior displacement of the barium filled stomach by the mass in the left lobe of the liver is clearly demonstrated on the contrast studies.

mitted to the North Carolina Baptist Hospital on July 11, 1961. The history revealed that she had been in good health until November, 1960, at which time she began having occasional episodes of nausea and vomiting. She had one episode of hematemesis in January, 1961, and was admitted to another hospital. Various studies failed to establish the etiology of the gastrointestinal bleeding and she was discharged. During the next few months, she had intermittent bouts of epigastric burning discomfort which was unrelated to meals. She also complained of frequent postprandial bloating which was relieved by medication but not by food. She lost approximately 10 pounds during this period of time.

The past history revealed a bout of rheumatic fever at the age of 19. She had a thyroid goiter removed in 1956. The remainder of the history was unremarkable.

The physical examination was negative except for a mass palpable 2 finger-breadths beneath the left costal margin, which was thought to be spleen.

The admission laboratory work revealed a normal white blood cell count, a hemoglobin of 11.8 gm. per cent and a hematocrit of 40 vol. per cent. The first platelet count was reported as 300,000. Liver function and electrolyte studies were within normal limits. The protein bound iodine was 4.4 μg. per cent. Chest roentgenograms, gallbladder series, and an electrocardiogram were interpreted as normal. An upper gastrointestinal series revealed a mass in the left upper quadrant which displaced the stomach (Fig. 1, *A* and *B*) posteriorly and to

the right. This was interpreted as most likely representing splenic enlargement. There was no evidence of peptic ulcer or esophageal varices. The barium enema and intravenous pyelographic studies were within normal limits except that a slight caudal displacement of the splenic flexure and left kidney by the left upper quadrant mass was noted. The small bowel series was normal. She was discharged with a diagnosis of splenomegaly of unknown etiology.

She was re-admitted on September 12, 1961, with complaints of constant left upper quadrant pain and intermittent attacks of nausea and vomiting. The vomitus had a "coffee ground" appearance but no bright blood was seen. The platelet count at this time was 65,000. Esophagoscopy was normal. A repeat examination of the stomach demonstrated the left upper quadrant mass to be unchanged; the stomach was still displaced posteriorly and to the right. The impression at this time was portal hypertension with splenomegaly and thrombocytopenia. She was transferred to the surgical service for exploratory laparotomy. At operation, the spleen was normal and a large cystic tumor was found which involved about 90 per cent of the left lobe of the liver. The portal pressure was recorded as 9.5 cm. of water. The right lobe of the liver was normal. A left hepatic lobectomy was successfully performed.

A few hours after surgery a copious amount of bloodstained fluid was noted coming from the drains which had been inserted at surgery. The hematocrit had dropped to 20 vol. per cent. She was returned to the operating room and re-explored. A few oozing points were noted on the raw edge of the liver and the peritoneal cavity contained approximately 1,500 cc. of bloody fluid. The bleeding points were controlled with sutures and the wound again closed. She received a total of 11 pints of blood during the two surgical procedures. Blood fibrinogen level at the time of surgery was slightly depressed and she also received 2 units of fibrinogen.

Her postoperative course was largely unremarkable except for a mild transfusion reaction. The platelet count rose to 165,000 by the tenth day. She was discharged to the care of her physician on October 4, 1961. She continued to do well at home until the onset of mild jaundice in February, 1962. She was again admitted to the hospital, where a diagnosis of serum hepatitis was made. Her platelet count on this admission was 250,000. A barium study of the stomach showed no abnormal impression upon that organ. An ulcer was seen in the duodenal bulb (Fig. 2) at this time. She made an uneventful recovery and returned home for further convalescence.



FIG. 2. Barium study on the last admission, which was 4 months after surgery, shows no abnormal impression upon the stomach. There is an ulcer demonstrated in the duodenal bulb.

DISCUSSION

Thrombocytopenia has been established as occurring in certain patients with hemangiomas of the skin and in one where the hemangioma was located in the colon.[1] It is not surprising to find it associated with a hemangioma of the liver. Hemangioma of the liver has been recognized with increasing frequency in recent years but a

correct preoperative diagnosis is extremely uncommon. In retrospect, the diagnosis might have been suggested in our case by the combination of a mass in the region of the liver, unexplained gastrointestinal symptoms, and thrombocytopenia. This triad is not pathognomonic, but should lead the physician to seriously consider the possibility of a hemangioma of the liver.

It is interesting to note that in July, 1961, the patient's platelet count was given as 300,000. However, in a few of the cases of skin angiomas reported, the platelet count was normal until the tumor was noted to be increasing in size. Only then did the thrombocytopenia develop. It would obviously be difficult to determine the rate of tumor growth in an internal organ such as the liver.

The single unequivocal episode of gastrointestinal bleeding in our patient, which occurred 9 months prior to surgery, is still unexplained. It is possible that an active peptic ulcer was overlooked on the barium meal studies at that time. An intriguing, but unproven, hypothesis is that the rate of platelet destruction within the hemangioma varies from time to time, perhaps related to the rate of the tumor growth. The occurrence of thrombocytopenia might be sporadic and intermittent. The thrombocytopenia could well cause a bleeding tendency. However, in our patient there was no mention of petechiae at the time of the hematemesis and melena. One of the cases of hepatic hemangioma reviewed by Shumacker had unexplained gastrointestinal hemorrhage. No platelet counts were given in that case.

CONCLUSION

1. A case of hemangioma of the left lobe of the liver with associated thrombocytopenia is reported. The thrombocytopenia is probably secondary to the destruction of platelets within the tumor. This case suggests the possibility of active and possibly sporadic growth of the tumor, producing an intermittent thrombocytopenia.

2. The presence of a palpable mass in the region of the liver, gastric displacement with gastrointestinal bleeding and vague symptoms, and thrombocytopenia should suggest the diagnosis of a hemangioma of the liver.

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CHOLECYSTOGRAPHY AS AN AID IN THE LOCALIZATION OF UPPER ABDOMINAL MASSES*

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IN THE investigation of upper abdominal masses, barium studies of the gastrointestinal tract and excretory urography are frequently the initial contrast examinations. While they serve to exclude lesions of the gastrointestinal tract and kidney respectively, their value in masses arising elsewhere is limited to spatial localization of the mass from displacement or encroachment on the contrast filled structures.[1,14,15]

More recently, specialized roentgenologic procedures such as aortography, presacral air insufflation, pneumoperitoneum, splenoportography and radioisotope studies have been advocated,[6,10] but these examinations are technically more difficult and therefore carry an added risk to the patient.

Since hepatic enlargements, gallbladder and pancreatic lesions constitute a large proportion of upper abdominal masses, cholecystography might be expected to be a useful adjunct in the diagnosis of such masses. Review of the literature on this subject reveals only one report advocating cholecystography[9] and this to exclude the gallbladder as the site of origin of the mass. In an attempt to assess the value of this examination, all cases of upper abdominal masses encountered in the Department of Radiology over the past 5 years were reviewed. A small series of 11 cases in which the diagnosis was established at surgery or autopsy was selected to illustrate the value of cholecystography in the diagnosis of upper abdominal masses (Table 1).

In view of the unusual cholecystographic findings, an additional case is included in this report although a definite histopathologic diagnosis is not available.

REPORT OF CASES

Case 1. M.B. This 68 year old male was admitted with a grossly enlarged liver, weight loss and right upper abdominal pain. There was no clinical jaundice.

An upper gastrointestinal study showed displacement of the stomach to the left and extrinsic pressure on the lesser curvature of the antrum. A barium enema study demonstrated inferior displacement of the hepatic flexure of the colon. Cholecystography revealed a well-functioning gallbladder which was horizontal in position and displaced laterally almost to the flank (Fig. 1). There was a smooth concave defect on the inferior aspect, measuring 8 cm. in length. The gallbladder showed no alteration in position on the prone, erect and decubitus roentgenograms.

Operation disclosed a large vascular tumor arising from the anterior surface of the liver extending inferiorly and medially. The pathologic diagnosis was primary carcinoma of the liver.

Case II. A.R. This 45 year old female entered the hospital with a firm, tender 4 cm. epigastric mass, generalized abdominal pain and intolerance to fatty foods. The patient was not jaundiced.

An upper gastrointestinal series demonstrated displacement of the stomach believed to be on the basis of hepatic enlargement. Cholecystography showed a well-functioning gallbladder which appeared elongated and displaced inferiorly, overlying the third and fourth lumbar vertebrae in the prone position (Fig. 2). There was also a smooth concave defect on the lateral aspect of the neck of the gallbladder approximately 3 cm. in length. In all projections, the defect was constant and the gallbladder was unchanged in position.

Operation disclosed a moderately enlarged liver studded with tumor nodules of varying size. The histopathologic diagnosis was primary hepatoma.

Case III (Fig. 3, *A* and *B*). A.B. This 53 year old female presented with a right upper quadrant mass and pain. There was no clinical jaundice. Ten months before this admission

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TABLE I

SUMMARY OF CASES

Case, Age and Sex	Clinical Findings	Cholecystographic Findings	Pathologic Diagnosis
I. M.B. 68 yr. male	Grossly enlarged liver; no jaundice	Gallbladder displaced laterally; fixed extrinsic defect	Primary carcinoma of liver
II. A.R. 45 yr. female	Firm epigastric mass	Gallbladder displaced medially; fixed extrinsic defect	Primary hepatoma
III. A.B. 53 yr. female	Right upper quadrant mass	Gallbladder displaced inferiorly; multiple fixed extrinsic defects	Primary hepatoma
IV. W.S. 59 yr. male	Marked hepatomegaly; no jaundice	Immobile gallbladder with large fixed filling defect	Primary carcinoma of liver with metastasis to the gallbladder
V. R.M. 49 yr. male	Perforated duodenal ulcer; tender mass on liver	Gallbladder displaced inferiorly; fixed deformed contour	Carcinoma of stomach with solitary metastasis to liver
VI. W.G. 56 yr. male	Right upper quadrant piriform mass	Emphysematous gallbladder with air-fluid level	Acute perforated emphysematous cholecystitis
VII. L.W. 27 yr. female	Tender tubular mass in right upper abdomen	Normal gallbladder laterally with an oval elongated opacity medially	Choledochal cyst
VIII. A.H. 51 yr. female	Enlarged liver, particularly left lobe	Gallbladder in normal position with fixed filling defect medially with central ulceration	None; probable carcinoma of gallbladder
IX. I.S. 41 yr. female	Firm mass in right upper quadrant	Gallbladder displaced medially with varying contour	Retroperitoneal leiomyosarcoma
X. E.C. 71 yr. female	Firm mass in right upper quadrant believed to be gallbladder	Gallbladder displaced superiorly with varying extrinsic defects	Retroperitoneal leiomyosarcoma
XI. C.O. 75 yr. female	Large mid-abdominal mass	Gallbladder mobile with varying displacements	Retroperitoneal leiomyosarcoma
XII. J.R. 61 yr. male	Right upper quadrant mass	Varying displacement of the gallbladder; medial bowing of upper portion of the common bile duct	Retroperitoneal leiomyosarcoma

she had been investigated for a questionable right upper quadrant mass but the upper gastrointestinal series, cholecystograms, and laminagrams of the renal areas were interpreted as normal.

During the present admission, barium studies revealed extrinsic pressure on the gastric antrum and inferior displacement of the hepatic flexure of the colon. A cholecystogram showed the gallbladder to be elongated and displaced inferiorly with the fundus at the level of the transverse process of L_5 (Fig. 3*A*). Three large scalloped extrinsic pressure defects were present on the lateral aspect of the gallbladder. The appearance of the gallbladder and of the defects showed no change in the prone, erect, and decubitus projections.

Laparotomy revealed the presence of a large tumor occupying almost the entire right lobe of the liver, which proved to be a primary hepatoma on histopathologic examination.

CASE IV (Fig. 4, *A* and *B*). W.S. This 59 year old male was admitted with hepatic enlargement, weight loss and abdominal pain. The serum bilirubin was normal. Three months before the present admission, a cholecystogram was interpreted as normal and a gastrointestinal series showed antral gastritis.

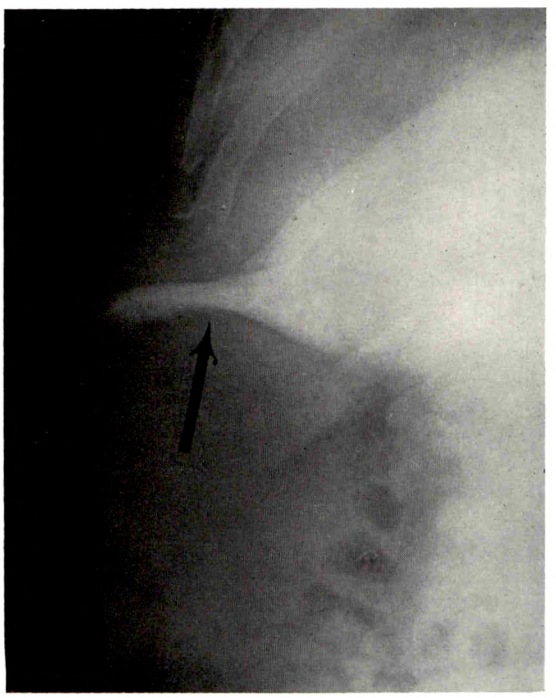


FIG. 1. Case I. The gallbladder is horizontal in position, displaced to the flank with a large, smooth extrinsic defect on the inferior margin (arrow). A large hepatoma arising from the anterior surface of the liver was found at surgery.

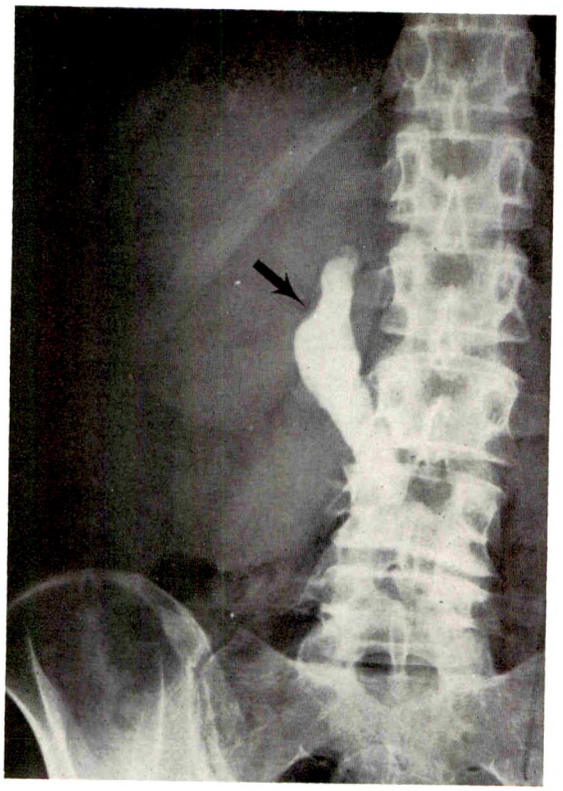
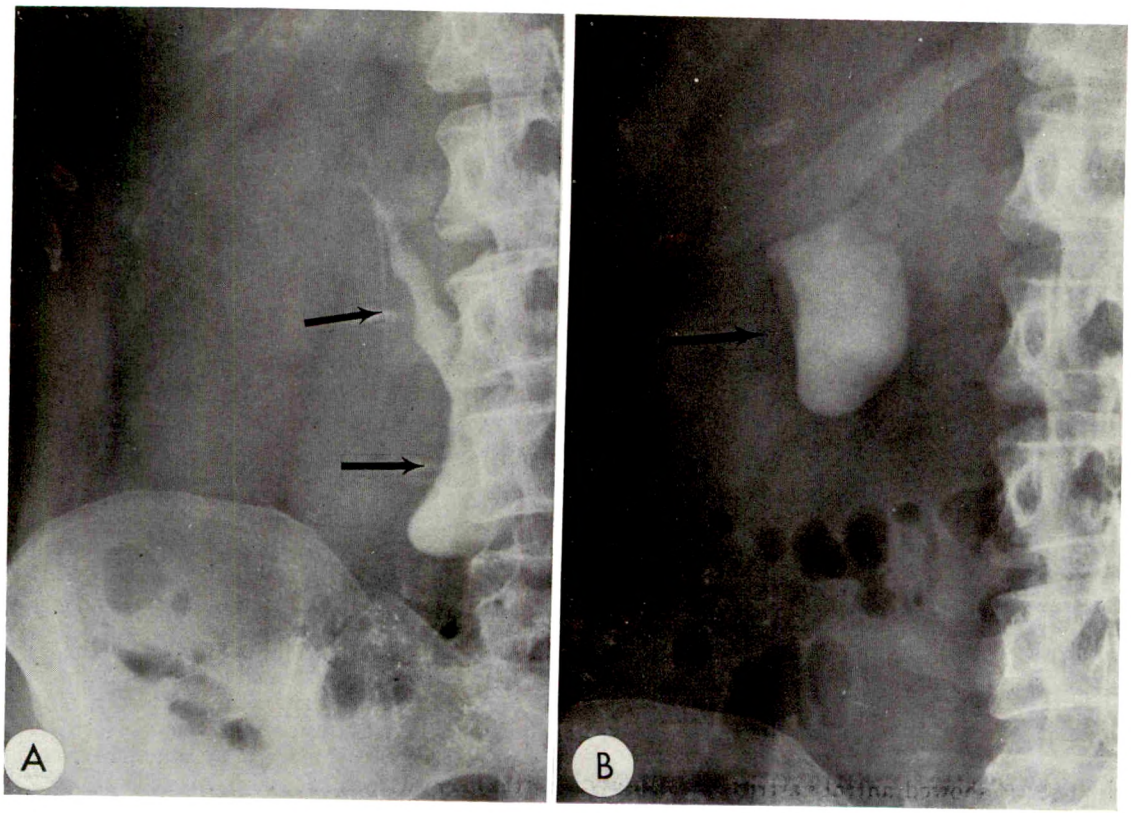


Fig. 2. Case 11. A smooth defect (arrow) is present on the lateral aspect of the gallbladder, which is displaced inferiorly and medially. At operation, primary carcinoma of the liver was found presenting as varying sized masses throughout the liver.

At the present admission, an upper gastrointestinal series demonstrated extrinsic pressure on the gastric antrum and on the second portion of the duodenum. A cholecystogram showed an irregular collection of contrast medium in a normally situated gallbladder (Fig. 4*A*), but the gallbladder showed no evidence of mobility in erect, prone and decubitus projections.

Percutaneous liver biopsy established a diagnosis of primary hepatoma, this diagnosis being confirmed at autopsy 2 months later. The gallbladder wall and lumen were invaded by the tumor.

Case v. R.M. This 49 year old male was admitted with a diagnosis of perforated duodenal



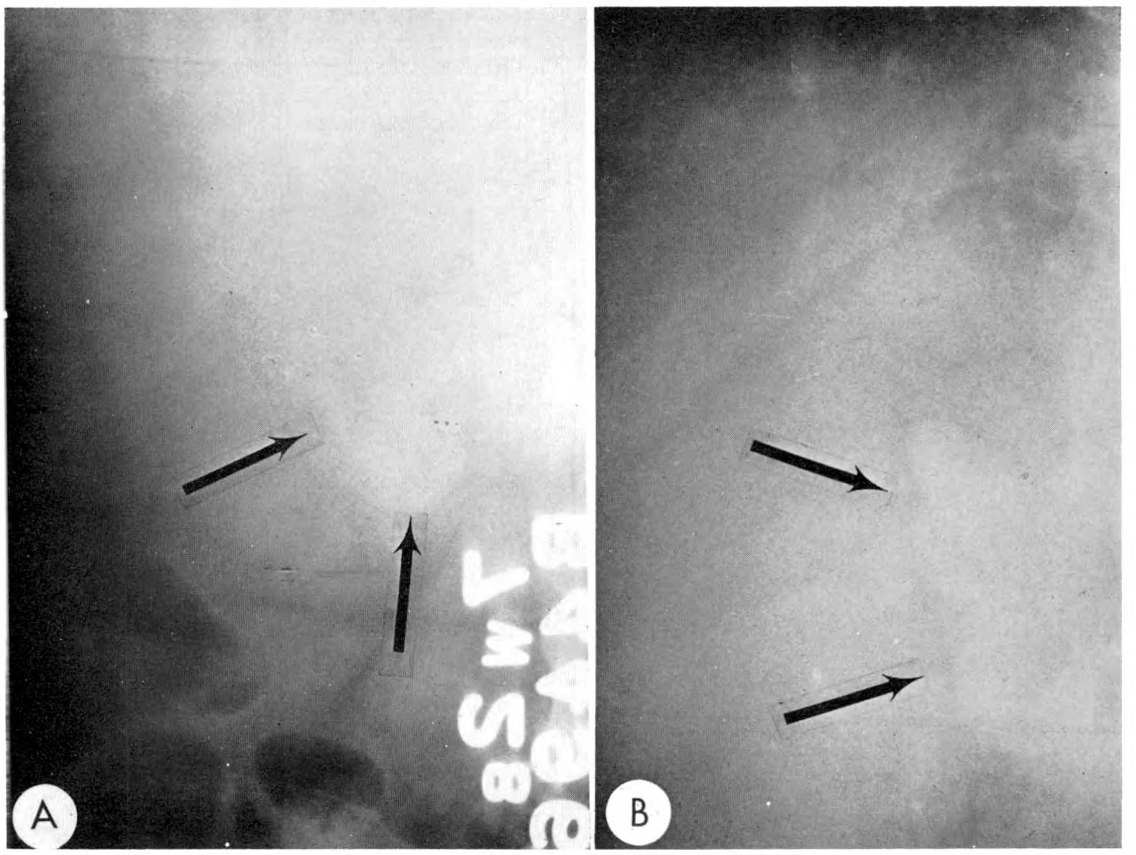


Fig. 4. Case iv. (*A*) An irregular collection of contrast medium is faintly visualized in the gallbladder (arrows) which remained fixed in all projections. Autopsy revealed gross infiltration of the gallbladder by a primary carcinoma of the liver. (*B*) A lateral decubitus roentgenogram done at the first admission demonstrating medial position of the gallbladder and a shallow defect on the dependent margin (arrows).

ulcer of 24 to 36 hours' duration. A limited upper gastrointestinal study showed deformity of the duodenal bulb with extravasation of contrast medium about the bulb. Hepatic enlargement was also noted on admission. In view of the patient's condition, conservative therapy was instituted.

Subsequently a pelvic abscess developed and was drained, but, in spite of this, pyrexia continued. A tender mass appeared on the anterior aspect of the liver, and progressive enlargement of the liver took place. As jaundice was absent, cholecystography was undertaken. This revealed a well-functioning gallbladder with the body and fundus in a horizontal position (Fig. 5). The gallbladder was displaced to the level of the body of L4 and showed no change in position or configuration in the various projections.

Laparotomy revealed a large necrotic mass in the right lobe of the liver and a small subphrenic fluid collection on the right. The patient died postoperatively and autopsy established the diagnosis of an enlarged liver with a massive solitary metastasis in the right lobe of the liver. A primary gastric neoplasm, 5 cm. in diameter,

Fig. 3. Case iii. (*A*) The gallbladder is displaced medially with 3 large scalloped defects on the lateral aspect (arrows). A large hepatoma of the right lobe of liver was found at operation. (*B*) Cholecystogram from the first admission demonstrating a single shallow defect (arrow) corresponding to the position of the scalloped defects noted on the second examination.

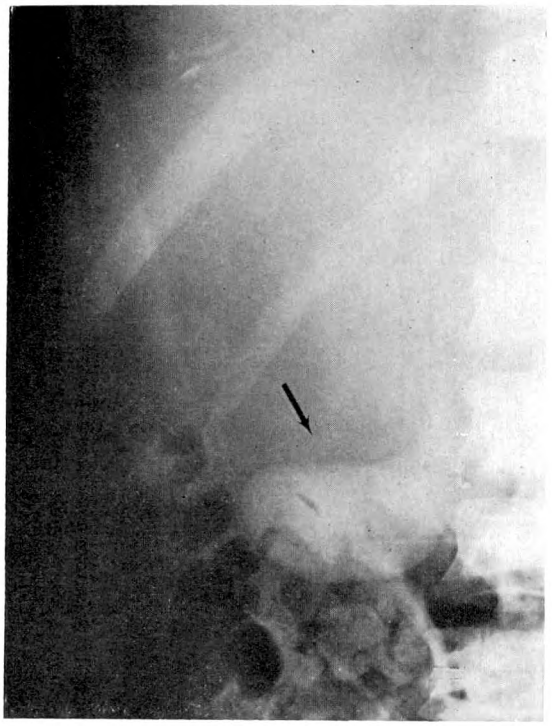


Fig. 5. Case v. The gallbladder appears "L" shaped with the fundus and body in a fixed position (arrow). At autopsy, the gallbladder was found adherent to a large necrotic metastatic tumor on the anterior surface of the liver.

was found in the fundus of the stomach posteriorly. A perforated duodenal ulcer with a resolving adhesive peritonitis was also present. The gallbladder was adherent to the liver and to the tumor but was not invaded by the tumor.

Case vi. W.G. This 56 year old Negro male was admitted with a short history of epigastric pain and a piriform mass in the right upper quadrant. The mass was 10 cm. in greatest dimension. The patient was a mild diabetic controlled by diet alone.

A survey roentgenogram of the abdomen showed no abnormality, and no soft tissue mass separate from the liver could be identified. With further localization of the tenderness to the right upper quadrant, cholecystography was undertaken 3 days after admission. The preliminary erect roentgenogram showed an enlarged emphysematous gallbladder with an air-fluid level (Fig. 6).

At subsequent surgery, an acute perforated emphysematous gallbladder was drained.

Case vii. L.W. This 27 year old Chinese female presented for the sixth time with a tender tubular mass in the right upper abdomen, associated with epigastric pain, nausea and vomiting. There was no jaundice though mild episodes of jaundice had occurred in the past. Previous barium enema examinations were reported as showing an area of segmental colitis in the proximal transverse colon.

An upper gastrointestinal series showed no abnormality. Cholecystography performed for the first time at this admission revealed a faint rounded opacity in the right upper quadrant

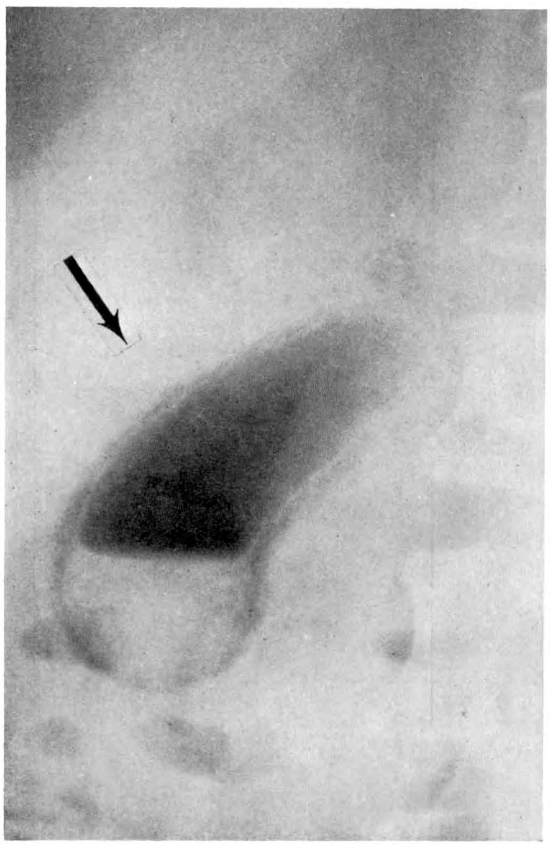


Fig. 6. Case vi. An erect roentgenogram demonstrating an emphysematous gallbladder (arrow) with an air-fluid level which proved to be a perforated emphysematous cholecystitis at surgery.

interpreted as gallbladder, and above and medial to this opacity another elongated oval opacity (Fig. 7). This was well delineated at its periphery but only faintly visualized centrally. A follow-up roentgenogram taken 24 hours later confirmed the initial findings and, in addition, several finger-like processes were noted at the upper limit of the oval opacity suggesting hepatic ducts *en face*. A subsequent intravenous cholangiogram showed similar findings and the distal part of the common bile duct was visualized and appeared of normal caliber.

Surgery disclosed a choledochal cyst, 5 cm. in width, with a normal cystic duct and gallbladder. The main hepatic ducts were grossly dilated. The transverse colon was normal in appearance.

Case viii. A.H. This 51 year old Negro female entered the hospital because of weakness and weight loss. The liver was enlarged and an extension inferiorly into the epigastrium was believed to be due to left lobe enlargement. There was no jaundice.

An upper gastrointestinal examination revealed extrinsic pressure upon the lesser curvature of the stomach believed to be due to hepatic enlargement. A barium enema study was normal. Cholecystography revealed a well-functioning gallbladder in a normal position. On the medial aspect of the gallbladder there was an irregular filling defect measuring 2 cm. across, with a central collection of contrast medium suggesting ulceration (Fig. 8). In the prone, erect, and decubitus projections, the defect appeared constant and the gallbladder displayed very limited mobility.

Unfortunately, the patient has so far refused surgery and discharged herself from the hospital, but carcinoma of the gallbladder is considered the most probable diagnosis.

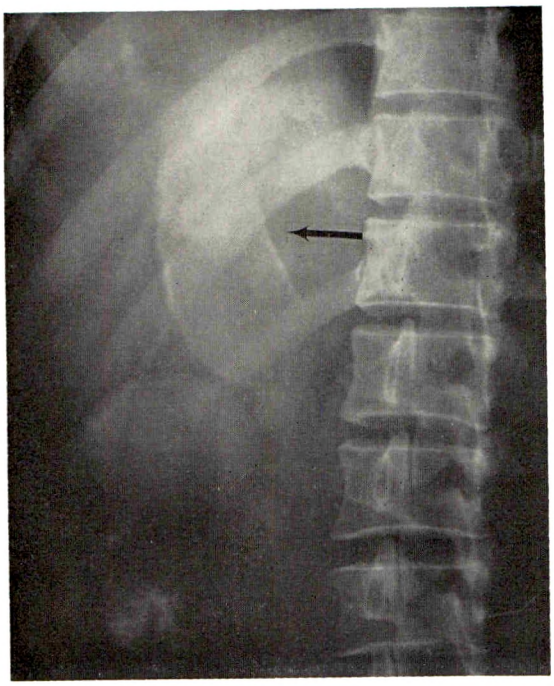


Fig. 7. Case vii. The gallbladder is visualized as a rounded opacity lateral in position. The medial, faintly visualized oval opacity (arrow) proved to be a choledochal cyst at surgery.

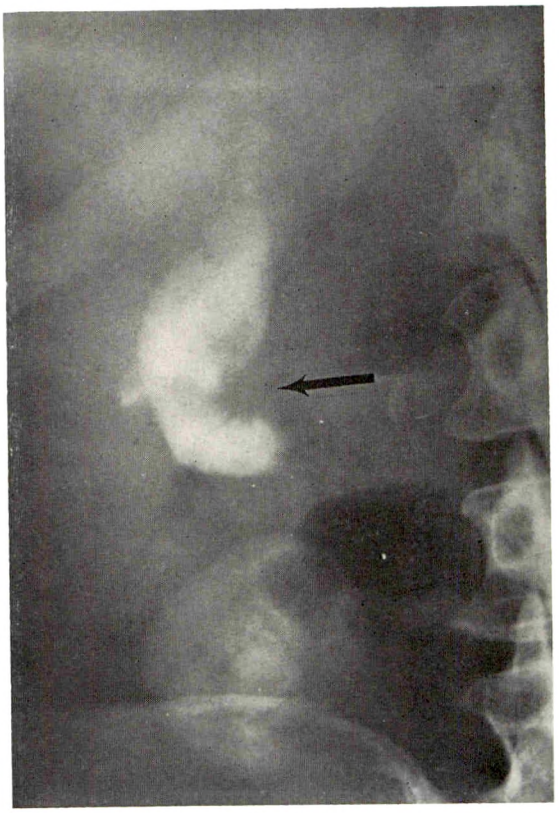
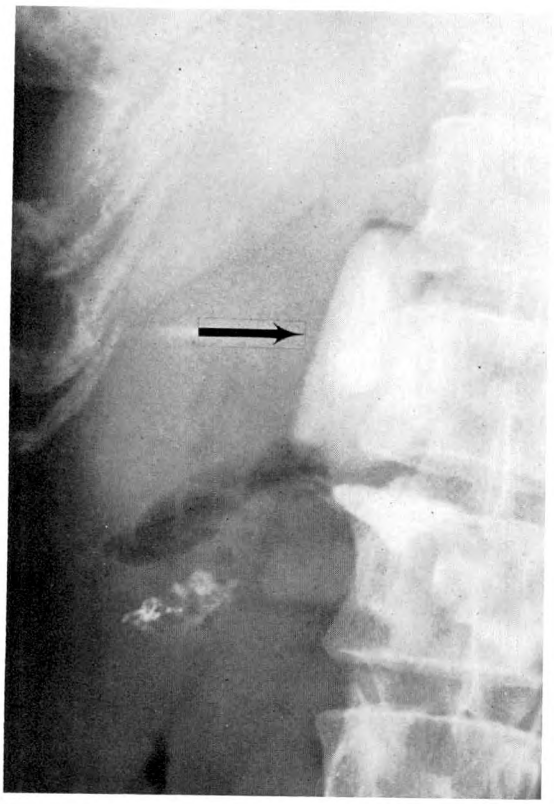


Fig. 8. Case viii. The gallbladder is well opacified and an irregular filling defect is noted medially with a central collection of contrast medium suggesting ulceration (arrow). Although not yet proven, the findings strongly suggest a carcinoma of the gallbladder.

Case ix. I.S. This 41 year old female presented with upper abdominal pain, nausea and a hard mass in the right upper quadrant. The mass was believed to be separate from the liver and there was no jaundice.



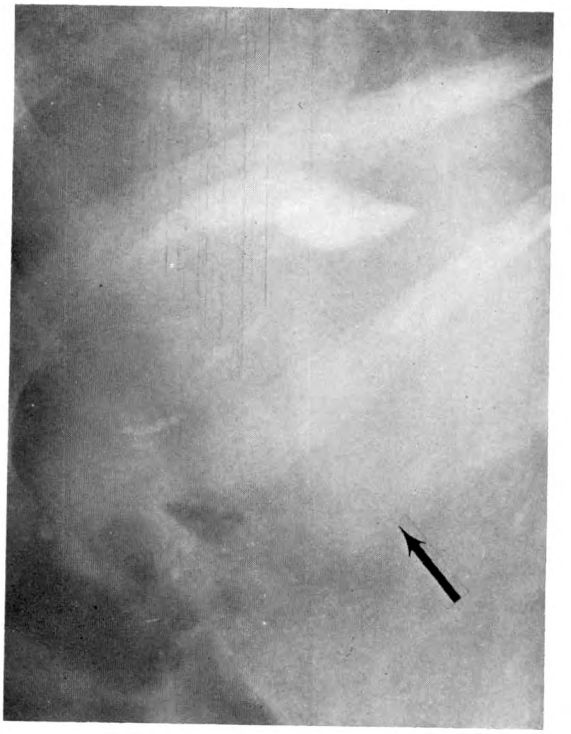


Fig. 9. Case IX. A prone roentgenogram showing the gallbladder displaced medially and folded on itself (arrow). A leiomyosarcoma involving the second portion of duodenum was found at surgery.

Intravenous urography revealed a soft tissue mass in the right upper abdomen which appeared separate from the right kidney. Only the upper third of the right ureter was visualized and there was a mild degree of distention of the collecting system on the right, due to mild compression of the ureter by the mass. A barium enema study showed no abnormality. Because the mass extended anteriorly, cholecystography was carried out. The gallbladder concentrated well but was displaced medially and folded on itself in various projections (Fig. 9). The contour varied slightly and the gallbladder appeared mobile.

Surgery disclosed a grapefuit sized mass involving the transverse mesocolon and wall of the second part of the duodenum. The pathologic diagnosis was retroperitoneal leiomyosarcoma.

Case X. E.C. This 71 year old female was admitted to the hospital with right upper quadrant pain, nausea and vomiting. There

Fig. 10. Case x. A large mass (arrow) is seen displacing the gallbladder superiorly. Concave defects are noted on the inferior surface of the gallbladder. Surgery disclosed a retroperitoneal leiomyosarcoma adherent to the right kidney.

was no jaundice. A firm mass believed to be gallbladder was palpable in the right upper quadrant.

A cholecystogram showed the gallbladder to be displaced upwards, and concave defects were noted on its inferior border (Fig. 10). In the various positions, there was slight variation in contour of the gallbladder and the gallbladder showed limited mobility. An intravenous urogram showed the right kidney to be displaced downwards by the mass which appeared separate from the kidney. A barium enema study showed no abnormality.

Laparotomy revealed a hard retroperitoneal mass involving the inferior vena cava and firmly adherent to the right kidney. The histopathologic diagnosis was leiomyosarcoma.

Case xi. C.O. This 75 year old female was admitted with an asymptomatic abdominal mass. There was no hepatomegaly or jaundice.

An upper gastrointestinal series showed a large extrinsic pressure defect on the greater curvature of the stomach and duodenal loop suggesting a pancreatic lesion. A barium enema study showed inferior displacement of the transverse colon and irregularity of the superior border. Cholecystography revealed a well-functioning gallbladder with marked mobility and displacement in the various projections (Fig. 11). The common duct was visualized and appeared in a normal position. No extrinsic defects were noted on the gallbladder.

Surgery disclosed a large cystic, vascular retroperitoneal mass with the base overlying the bifurcation of the aorta and distal inferior vena cava. The pathologic diagnosis was retroperitoneal leiomyosarcoma.

Fig. 11. Case xi. The gallbladder is seen displaced to the flank by a large mass (arrow). In other projections, the gallbladder demonstrated additional displacements and the common duct was visualized and appeared in normal position. The pathologic diagnosis was retroperitoneal leiomyosarcoma.

Case xii. J.R. This 61 year old white male complained of a right upper quadrant mass associated with a weight loss of 20 pounds in the past 6 months. The patient was not jaundiced.

Urograms showed a well-defined soft tissue mass in the right upper quadrant inseparable from the liver shadow. The lower pole of the right kidney was displaced slightly away from the mid-line, and though the right calyces and renal pelvis were normal, only the upper third of the right ureter was visualized and this appeared very tortuous. There was stasis of the contrast medium in the upper ureter.

A barium enema examination showed inferior displacement of the proximal third of the transverse colon, and on the lateral projection, the mass encroached on the posterior aspect of the transverse colon.

The gastrointestinal study findings were of considerable interest. The stomach was normal, but the duodenal cap exhibited a smooth extrinsic defect on its inferior border in some projections, but this was not visible when the patient was supine. Inspection of the roentgenograms showed that the defect was in fact due to a grossly displaced gallbladder (Fig. 12*A*), which, in the supine position, moved away from the duodenum. The most significant finding was an area of ulceration in the second portion of the duodenum, 3 cm. below the vaterian ampulla (Fig. 12*B*). The crater measured 1 cm. in diameter and the adjacent mucosa showed stretching and distortion of its folds.

Cholecystography, performed in conjunction with the gastrointestinal study, revealed an extremely mobile gallbladder which at times occupied a normal position and at other times overlapped the lumbar spine. Extrinsic defects were produced on the contour of the gallbladder by the adjacent mass. In addition, the common bile duct was clearly visible and showed medial bowing in the upper third of its course (Fig. 13).

Laparotomy confirmed the preoperative diagnosis of leiomyosarcoma of the duodenum, the resected mass measuring 12×8×10 cm.

DISCUSSION

Several interesting features are illustrated by this small group of cases which

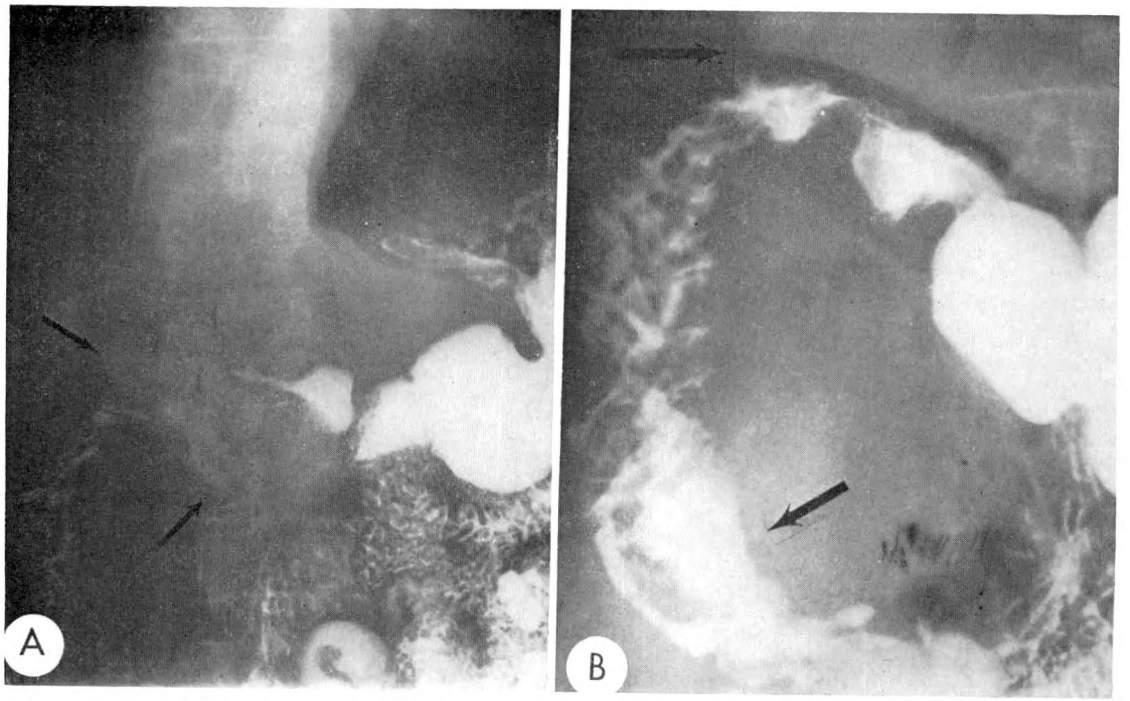
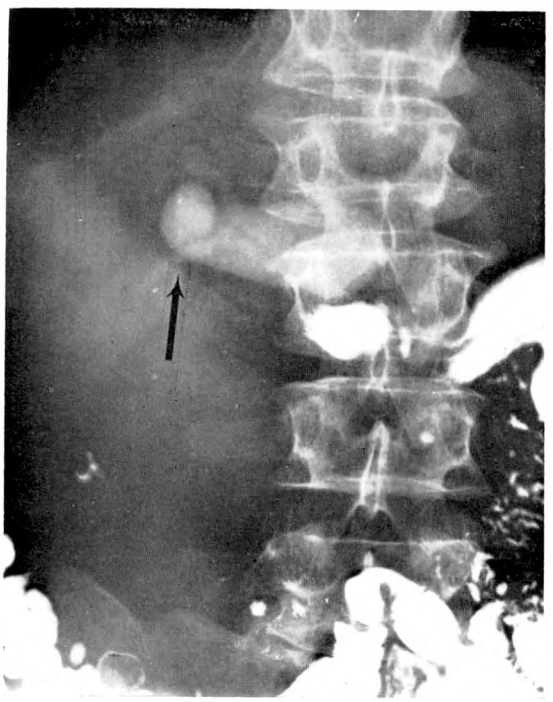


Fig. 12. Case xii. (*A*) Prone roentgenogram from combined cholecystography and upper gastrointestinal series. Note the displaced gallbladder (arrows) producing a concave defect on the inferior border of the duodenal bulb and the apparent widening of the duodenal loop suggesting a pancreatic lesion. (*B*) Supine roentgenogram showing the gallbladder (arrow) adjacent to the superior aspect of the duodenal bulb. Note the ulceration of the second portion of the duodenum (arrow) corresponding to the site of origin of a leiomyosarcoma.



includes masses of hepatic, biliary tract and retroperitoneal origin.

Hepatic Masses. Four cases of primary hepatoma (Cases i–iv) and one of metastatic liver disease (Case v) are presented.

Case iii is of interest in that review of the cholecystogram made on the first admission revealed a single shallow defect on the lateral aspect of the gallbladder (Fig. 3*B*) which probably indicated an early stage of the lesion, as it corresponded in position to the subsequent multiple scalloped defects demonstrated on the second examination. At that time, barium studies and laminag-

Fig. 13. Case xii. Prone roentgenogram from the cholecystography illustrating another displacement of the gallbladder and, in addition, the common duct is clearly visualized (arrow) and is bowed medially in its upper third.

raphy of the right upper quadrant failed to delineate a mass.

Case IV also had normal barium studies on the first admission. The cholecystogram at this time, however, showed a gallbladder which remained in a medial position, and, on the decubitus roentgenogram, a shallow extrinsic concave defect was noted on the dependent margin (Fig. 4*B*). Although overlooked at the time, this may have been significant as the gallbladder subsequently became contracted and absolutely fixed in position. Filling defects within the lumen were found at autopsy to be due to direct involvement of the gallbladder by the tumor.

Case V was believed to be a perforated duodenal ulcer with a subphrenic abscess until cholecystography was performed. The findings on this study were consistent with an intrahepatic mass which was confirmed at surgery and proved at autopsy to be a metastatic lesion. The primary lesion in the stomach could not be identified on review of the limited gastrointestinal series performed on admission.

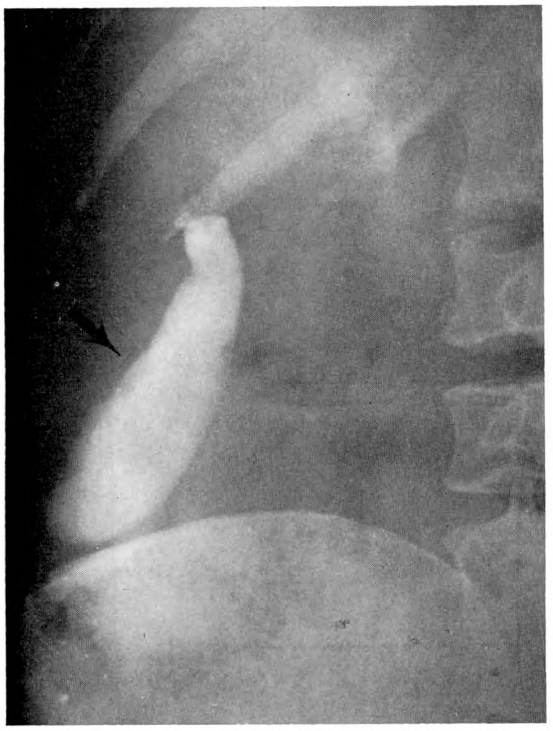


FIG. 14. A case of polycystic disease of the liver. Note the multiple defects (arrow) on the lateral aspect of the gallbladder.

In all of the cases of primary and secondary liver tumor, the gallbladder showed extrinsic defects which remained constant. Fixation of the gallbladder was observed in the prone, erect and lateral decubitus positions. There were, as would be expected, no differential features between the primary and metastatic lesions, as it is believed that any intrahepatic mass may produce these findings. Geist[8] and Gambill and Hodgson[7] have reported similar findings in cystic liver disease and we have encountered a case of polycystic disease of the liver with the same cholecystographic findings (Fig. 14). These lesions can usually be differentiated by their clinical course.

Biliary Tract Masses. Case VI, though having a palpable mass on admission, showed no abnormality on a survey roentgenogram of the abdomen. The survey roentgenogram of the cholecystography, 3 days later, produced the first evidence that the mass was of gallbladder origin. This latent period in emphysematous cholecystitis should be borne in mind.

An erroneous diagnosis had been made on 5 prior admissions in Case VII because cholecystography had not been performed in the investigation of the right upper quadrant mass. This study provided the specific diagnosis of the mass. Recently, an increasing number of reports of the demonstration of choledochal cysts on cholecystograms have been appearing in the literature.[5,11,13]

Although not yet proven, Case VIII most probably represents a carcinoma of the gallbladder. Isolated reports of filling defects in the opacified gallbladder in cases of carcinoma of the gallbladder have appeared in the literature;[2,4,17] however, none of these describes the suggestive ulceration visualized in this case. Considering the rarity of preoperative diagnosis of gallbladder carcinoma by any procedure,[12,16] and the frequency with which it is associated with an upper abdominal mass, cholecystography would appear to be the only available method for earlier diagnosis.

Retroperitoneal Masses. Case IX, as a result of barium studies, was believed to be a pancreatic mass, but the demonstration of an undisplaced common bile duct on cholecystography made this unlikely. The mobility and displacement of the gallbladder suggested the extrahepatic location of the mass.

Case XII illustrated the value of cholecystography in two respects. First, since the patient had never been jaundiced, the demonstration of the displaced common bile duct was the only indication of involvement of this structure by the mass. Secondly, an erroneous impression of a pancreatic lesion at fluoroscopy was dispelled when cholecystograms showed the extrinsic defect on the duodenum to be due to the grossly displaced gallbladder.

All the retroperitoneal masses showed displacement of the gallbladder and most had extrinsic defects on the contour. The distinction from intrahepatic lesions was made, however, by the fact that the gallbladder remained mobile and the defects varied in configuration. Extrinsic defects on a mobile gallbladder have been recorded in a few isolated reports of adrenal[19] and pancreatic[3] lesions and choledochal cyst.[18]

In this group of cases, barium studies demonstrated nonspecific encroachment on the stomach consistent with hepatic enlargement in 6 cases, while in 3 cases the studies were normal. In 2 cases, barium studies were not performed. In only 1 case (Case XII), did this examination yield specific information of ulceration of the gastrointestinal tract.

Urography performed in the 3 patients with retroperitoneal lesions confirmed the location of the mass, but gave no indication of the site of origin.

Cholecystography, on the other hand, indicated the intrahepatic nature of the lesion in Cases I–V and gave a specific diagnosis in Cases VI, VII and probably Case VIII. In the retroperitoneal lesions, it merely confirmed the presence of the mass, but in Case XII elucidated the nature of a confusing impression on the gastrointestinal study as well as demonstrating involvement of the common bile duct by the mass.

CONCLUSIONS

From this group of cases it is concluded that cholecystography is a useful adjunct in the diagnosis of upper abdominal masses.

1. Intrahepatic lesions produced extrinsic defects on a fixed gallbladder, the configuration of the gallbladder being constant.
2. Extrahepatic masses displaced or indented the gallbladder, but the defects were not constant and the gallbladder was freely mobile.
3. Unsuspected gallbladder lesions may be detected.
4. Involvement of the common bile duct by the mass may be demonstrated.
5. The nature of confusing extrinsic defects observed on gastrointestinal studies may be clarified.

The examination should be considered in cases with any upper abdominal mass, including hepatic enlargement, provided jaundice is absent.

SUMMARY

The value of cholecystography in the diagnosis of upper abdominal masses has been illustrated by the presentation of 12 cases. These cases include masses of hepatic, biliary tract and retroperitoneal origin. By virtue of the demonstration of various displacements and alterations in the contour of the opacified gallbladder, it is concluded that cholecystography is a useful roentgenologic examination in the diagnosis of upper abdominal masses.

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ORAL CHOLEDOCHOGRAPHY IN THE POSTCHOLECYSTECTOMY PATIENT*

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ORAL cholangiography or choledochography in the postcholecystectomy patient has not received as much acceptance as the intravenous techniques, largely due to the lack of a good method. A procedure will be presented that has produced studies of diagnostic quality in 76 per cent of patients during a period of 3 years. Most investigators have felt the need for further improvement in diagnostic accuracy; particularly if this improvement could be made via the oral route, which should normally yield less serious systemic toxicity.

PROCEDURE

Starting with the method as developed and reported by Twiss *et al.*[1] in 1955 and using their research material relating to the maximum appearance times of iopanoic acid (Telepaque*) in the duct system, a shorter and more concise technique was developed. A more recent report by Twiss and Gillette[2] indicates that they also have shortened their original procedure. Their procedure and the one being presented here are quite similar at the present time, even though they were developed independently. Larger than normal amounts of oral radiopaque are used in the absence of the normal concentrating area—the gallbladder.

A total of 24 tablets of iopanoic acid is used; 12 tablets are taken the evening prior to examination. The first evening dose, 6 tablets, is administered 14 hours before the examination; 30 minutes later 6 more tablets are taken. The remaining 12 tablets are likewise taken a half hour apart, 6 tablets at each interval, starting 4 hours before the examination. Two hours after the last tablets have been partaken, the patient is given 2 drams of paregoric in water or $\frac{1}{6}$ gr. of morphine sulfate to contract the sphincter of Oddi.

Preparation of the patient and positioning are the same as for routine cholecystography, including the fat-free supper and no subsequent food or liquids until the examination is completed. Roentgenograms are taken at hourly intervals up to 4 hours, or until the duct system is visualized. Since the visualization is not progressive, a fatty meal is given once the ducts are visualized and another set of roentgenograms are taken after 20 minutes. The fatty meal has improved the visualization in some cases. If there is no visualization after the fourth set of roentgenograms, or at the end of 4 hours, the examination is terminated.

REACTIONS

Reactions to the large amount of opaque medium were no more frequent or severe than with the smaller amount used for routine cholecystography and were not a problem. With the original extended 2 day procedure, the reactions were more frequent, but seemed to be due more to the length of the procedure and the restricted diet than to the medium used. In general, the procedure was well tolerated by all patients in all age groups.

EVALUATION OF EXAMINATIONS

Ninety-two patients were examined by this method, all of whom had had a cholecystectomy. No specific diagnosis had been made prior to the examination.

Evaluation of the quality of the examination was based entirely on the films and included two major groups: nondiagnostic films and films of diagnostic quality. Under the nondiagnostic grouping were included

* Telepaque-Brand of Iopanoic Acid—Winthrop Laboratories.

* Presented to the Wisconsin Radiological Society Annual Meeting, September 12, 1959.



Fig. 1. Normal oral choledochogram.



Fig. 2. Normal choledochogram showing a short cystic duct stump.

Table I

DIAGNOSTIC QUALITY OF STUDIES IN 92 CASES

	No. of Patients	Per Cent
Diagnostic Visualizations		
Excellent	25	27.2
Very satisfactory	24	26.1
Satisfactory	21	22.8
Total	70	76.1
No visualization		
Pathologic cause	9	9.7
Unknown cause	13	14.2
Total	22	23.9

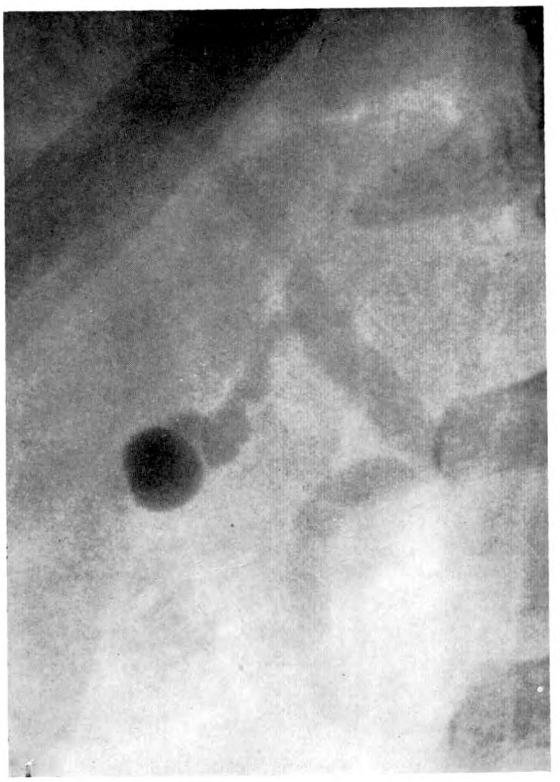


Fig. 3. Choledochogram showing a dilated residual cystic stump.



Fig. 4. Choledochogram showing a cystic stump with a calculus.



Fig. 6. Choledochogram showing a "residual" gallbladder with a calculus.



Fig. 5. Choledochogram showing a cystic stump with a fibroma.

all films with insufficient visualization or no visualization. Those considered to be of diagnostic quality were classified according to the degree of visualization as excellent, very satisfactory, or satisfactory. The results are shown in Table 1; 76 per cent of the studies resulted in diagnostic visualization of the duct system.

In the nonvisualizing or nondiagnostic group (24 per cent), there was apparent pathologic cause for the lack of visualization in 10 per cent of the examinations. Included were cases of duodenal ulcer, scarring and deformity of the duodenum, all with gastric retention, and gastric retention of the opaque medium of indeterminate cause. In the remaining 14 per cent, there was no apparent cause for the lack of visualization on the roentgenograms. Complete liver profile studies were made of all

the patients in this group to aid in the determination of the site of the obstruction. Two patients with severe obstructive jaundice were examined and as expected there was no visualization.

DIAGNOSTIC FINDINGS

No attempt will be made to present case reports; however, 23 per cent of the patients exhibited findings which were considered pathologic. Figure 1 shows a normal postcholecystectomy choledochogram; Figures 2 through 6 demonstrate some of the pathologic findings that were proven surgically or by autopsy. Of particular interest was the case illustrated in Figure 5, where a suspected noncalcified residual calculus in the cystic duct proved to be a fibroma of the tip of the cystic stump. A residual cystic stump over 4 cm. in length was considered pathologic whether it was dilated or not. The problem of the cystic duct stump as a cause of symptoms and the residual "reformed", or "recurrent" gallbladder will not be discussed, although mention should be made that dilute but completely dissolved opaque medium in the duodenal cap can resemble but is easily differentiated from the residual or "recurrent" gallbladder.

CONCLUSION

A modified technique for oral cholangiography in postcholecystectomy patients has been presented that is well tolerated. In the reported series diagnostic choledochograms were obtained in 76 per cent of 92 patients studied during 3 years. This procedure is an additional aid in the evaluation of the postcholecystectomy syndrome.

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INTERPRETATION OF THE PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAM*

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THE technique of percutaneous transhepatic cholangiography was first described by Carter and Saypol[1] in 1952 and then by Murick *et al.*[5] in 1953. The indications for the procedure were enumerated by Kidd[4] in 1956. Additional work with case reports has been contributed by other investigators in the field.[2,7,8] It is the purpose of this paper to discuss the diagnostic possibilities of the percutaneous transhepatic cholangiogram from a roentgenographic aspect.

We shall present our own experience in a series of 35 cases[9] as well as those points of diagnostic importance previously discussed in the literature.

TECHNIQUE OF STUDY

Of the 35 studies in this series, 34 were carried out under local anesthesia, which we believe to be the preferred method, and one under general anesthesia. With the patient in the supine position, the needle is inserted in the right hypochondrium at an angle of 45 degrees to the horizontal and in line with the mid-clavicular line on the right. Angulation is toward the mid-clavicular line on the left. The needle is inserted to a depth of 4 to 5 inches and gradually withdrawn with frequent aspirations. If blood is obtained than the needle is simply withdrawn slightly and again aspiration is carried out until bile is obtained. The opaque material may then be injected. We have used both hypaque* and cholografin† in this study. The entire procedure is carried out under fluoroscopic control with spot roentgenograms being made intermittently, usually after injection of each 10 cc. of medium. This is very important in carrying out a good study for establishing location and in obtaining sequence of visualization of the various elements of the biliary tract. A total of 30 to 60 cc. of material was generally injected. The needle is then removed and roentgenograms are made in anteroposterior, lateral and both oblique projections. A 15 minute anteroposterior roentgenogram is obtained to evaluate emptying of the biliary system. The central ray is usually directed at the region just to the right of the xyphoid portion of the sternum. The proper location of the central beam may be determined fluoroscopically.

COMPLICATIONS

In the series of patients studied at this institution, there were no deaths due to the procedure. There was one gallbladder perforation, requiring laparotomy and 2 cases of extravasation of opaque material into the peritoneal cavity, one above the liver and the other below. These patients recovered without incident. There was one case of tension pneumothorax due to puncture of the diaphragm and lung. The patient did well with insertion of an intercostal catheter. Because we found a high incidence of positive bacteriologic cultures from the bile obtained, we routinely used antibiotics in the postoperative period. There were 8 failures of 43 attempts at bile duct injection. This compares with results of other investigators.[8]

GENERAL DISCUSSION

The roentgenographic points of diagnostic interest will be described under a disease

* Obtained from Winthrop Laboratories, New York, New York.
† Obtained from Squibb & Sons, New York, New York.

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classification; however, there are a few general factors which should be brought out prior to any specific discussions.

The pressure on the obstructed ductal system usually found on initial puncture was about 120 mm. of saline. It was noted that about 30 to 60 cc. was sufficient to fill the dilated ductal system; the addition of more contrast medium did not distend the ducts but filled the smaller and more peripheral radicals. Proof of this phenomenon was obtained by serial spot roentgenograms made during injection.

The left hepatic duct frequently had to be filled by placing the patient in the right anterior oblique position on the table with the left side down.

It was noted that often the stomach was visualized in those patients in whom there was patency of the biliary system. We are not certain as to the significance of this, although it would seem that such might occur when the gallbladder contracts during normal activity. It is possible that the patient's general systemic condition at the time of the procedure might contribute to the reflux of the medium into the stomach because of gastric and possible duodenal atony.

ROENTGEN FINDINGS

OBSTRUCTION DUE TO CALCULI

Generally, a rounded defect can be seen in the common duct (Fig. 1). Frequently the opaque material may pass around the stone and through the common duct even though clinically the patient appears to have complete obstruction. The distal end of the common duct may show a concave or flattened appearance. There may be other stones present in the hepatic ducts. All ducts may show dilatation, including the fourth and fifth divisions, and also some tortuosity. The degree of tortuosity and dilatation is dependent upon the duration and extent of the obstruction. The pancreatic duct generally does not visualize as there probably is insufficient pressure beyond the stone for such to occur.

Norman[6] in 1951 described the roentgenologic appearance of biliary tract stones and discussed the differential diagnosis. Air bubbles must be taken into consideration. They present as round filling defects but usually shift about when the position is changed and may disappear on subsequent injections. These probably can be avoided by proper techniques. We failed to encounter any in our cases. Mucus floccules usually are irregular and somewhat elongated (Fig. 2). We have seen these almost along the entire length of a biliary radical giving the appearance of an air contrast study to that portion of the tree. Blood clots, as a rule, are not present in the biliary system.

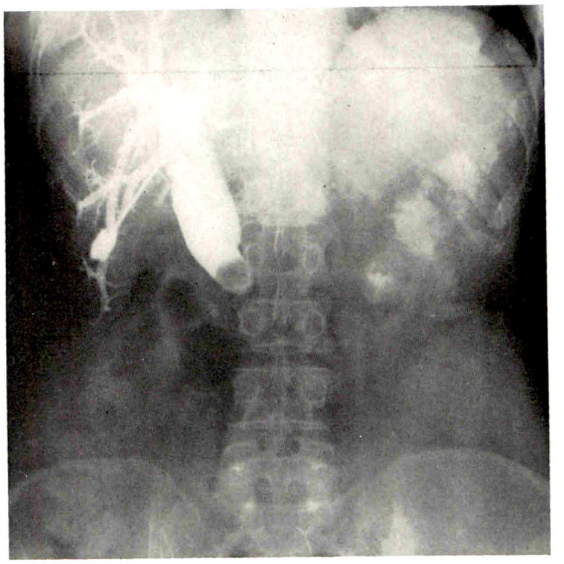


Fig. 1. Obstruction of the common duct due to stone. Note the rounded filling defect in the distal end of the common duct. This proved to be a large non-radiopaque calculus.

OBSTRUCTION DUE TO BILE DUCT STRICTURE

The distal end of the obstructed duct is usually convex, possibly even pointed (Fig. 3). There may be good visualization of the pancreatic duct. We encountered 4 such instances in the 7 strictures studied. This did not appear to be related to the exact location of the stricture. We did not note any dilatation of the pancreatic ducts in our cases. The biliary tree was dilated and the radicals filled well, but the marked degree

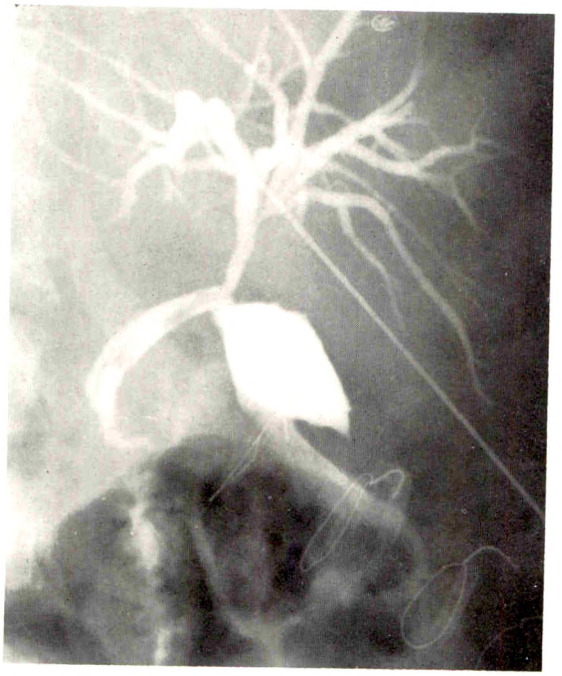


Fig. 2. Partial obstruction of the common hepatic duct. Note the presence of the fistula extending anterior from the common duct. The patient had undergone a cholecystectomy recently.

of tortuosity observed with calculi was not seen in this group.

BILIARY FISTULAS

We found several unsuspected biliary fistulas (Fig. 2). These were into the adjacent small bowel or into walled-off pockets lying anterior or lateral to the common duct. These pockets may be differentiated from the gallbladder by injection of additional material or by multiple views. Most of these patients were, however, post surgical and absence of the gallbladder was known prior to the study. Transhepatic cholangiography is the best nonsurgical method for demonstrating these unsuspected fistulas.

CARCINOMA OF BILIARY SYSTEM

The changes seen here are usually proximal to the distal end of the common duct and present as gross irregularities (Fig. 4). Filling defects in the ducts may be irregular and usually multiple and are unlike the rounded defects seen with biliary calculi.

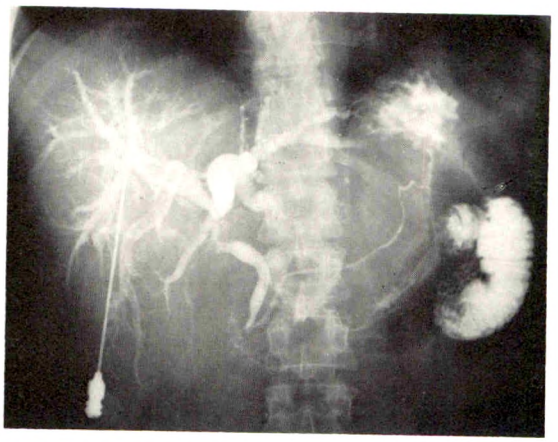


Fig. 3. Partial obstruction due to stricture of the common hepatic duct with some degree of obstruction in the channel common to the bile duct and the pancreatic duct. Mucus floccules may be seen in the dorsocaudal group of ducts, giving a double contrast type study.

There generally is distortion of the biliary tree by the tumor mass. Complete obstruction may or may not be present. The degree of dilatation of the ducts depends upon the completeness of obstruction of the hepatic or common bile ducts. The pancreatic duct

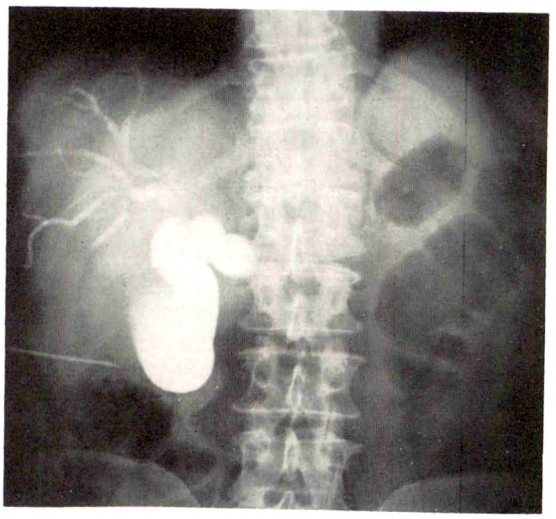


Fig. 4. Carcinoma of the biliary tree. Note the irregular partial obstruction of the hepatic duct. Some of the opaque material passed around the obstructed area into a dilated gallbladder and cystic duct and apparently into a dilated common duct. The absence of marked dilatation of the hepatic radicals suggests that the obstruction is not complete.

usually does not fill. Liver abscesses may also be encountered in these patients.

HEPATIC ABSCESS OR ABSCESSES

The needle aspirate may be that of pus rather than blood or bile. This would establish a diagnosis of suppurative infection and the possibility of an abscess should be strongly considered. One may inject the abscess cavity directly and thus visualize the extent of the excavation; however, this must be differentiated from intrahepatic extravasation. An abscess cavity appears to be more clearly defined and delineated than the intrahepatic extravasation of opaque material (Fig. 5). We encountered only one case of intrahepatic extravasation in the entire series and this was limited to a very small area. We found one case with a solitary intrahepatic abscess, but several cases with multiple small abscess cavities. These resembled ill-defined grapes on a vine with each cavity projecting off the end of a fifth division radical (Fig. 6). All cavities were of approximately the same size and were found only in patients with a primary disease of carcinoma producing obstruction. At autopsy, these proved to be pyogenic abscesses and not areas of necrosis in tumor nodules as one might possibly suspect.

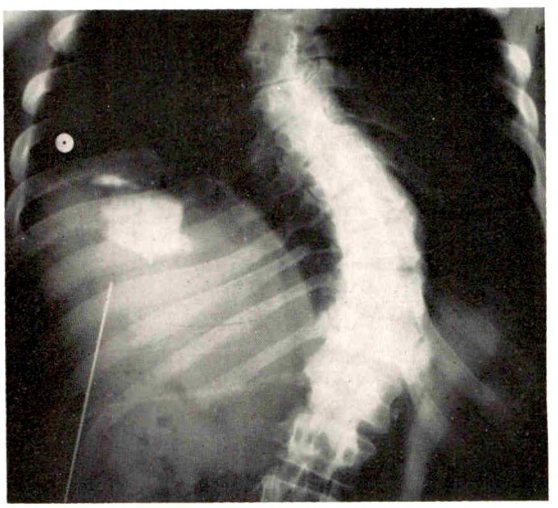


Fig. 5. Hepatic abscess. Note the clear delineation of the opaque material in the liver. This represented an abscess which communicated with the pleural cavity on the right. *Mycobacterium tuberculosis* was cultured from this cavity aspirate.

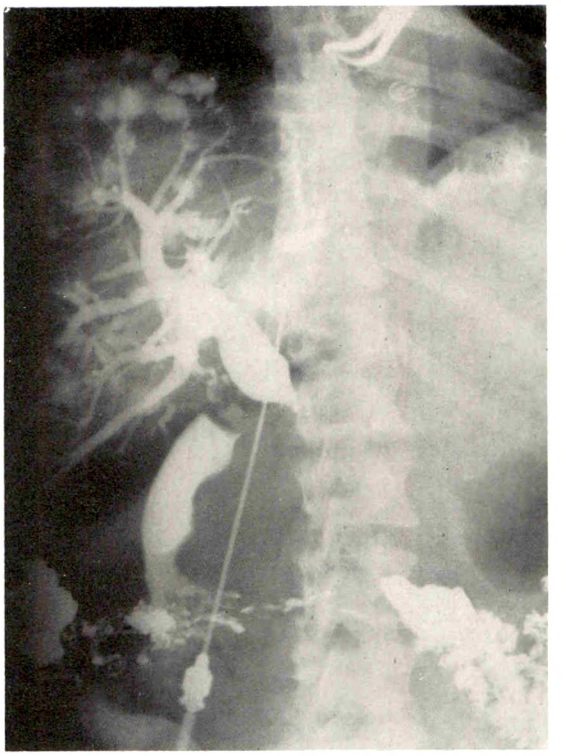


Fig. 6. Multiple hepatic abscesses in a patient with common duct obstruction secondary to carcinoma of the pancreas. The patient also had a cholecystojejunostomy because of the neoplastic involvement. Autopsy revealed widespread tumor; however, the cavities in the liver were pyogenic and not neoplastic in origin. Note also the small area of intrahepatic extravasation near the site of the injection.

CIRRHOSIS OF THE LIVER

This disease may be divided into 2 stages:

1. The stage of fat infiltration associated with liver enlargement (Fig. 7). In such instances the common duct is usually normal in size and without evidence of obstruction. The biliary radicals are elongated, very thin, and there is poor filling of the fourth and fifth division radicals. Much difficulty was encountered in obtaining a satisfactory bile duct puncture in these patients. This concurs with the experience of others[2] and is probably due to the diminished caliber of the ducts.

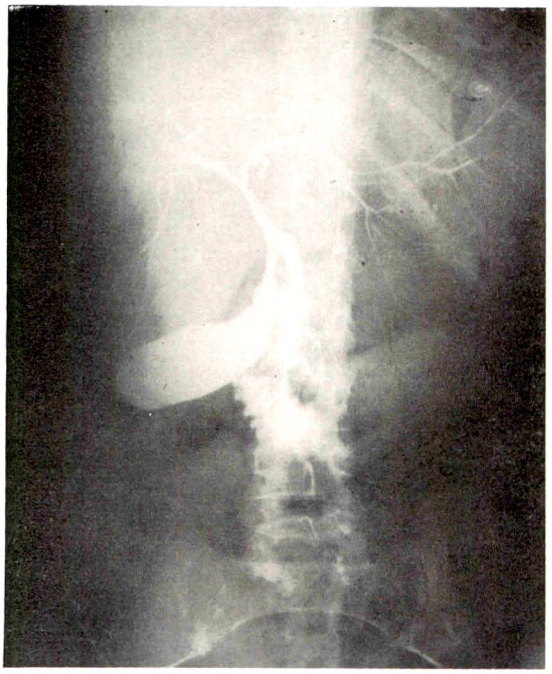


Fig. 7. Fat-infiltrated liver. Note marked enlargement of the liver with elongation and narrowing of the hepatic ducts. This patient was found to have cirrhosis with fat infiltration producing hepatomegaly.

2. The second stage is fibrotic cirrhosis with a decrease in the size of the liver. Here, the common duct shows no evidence of dilatation unless other conditions are superimposed on the existing cirrhosis. The smaller bile ducts show shortening and

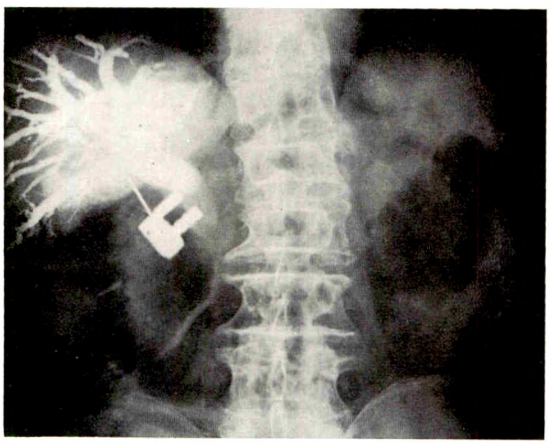


Fig. 8. Fibrotic cirrhosis. Note marked contracture of the liver with shortening of the ducts. There is dilatation secondary to obstruction produced by carcinoma of the pancreas.

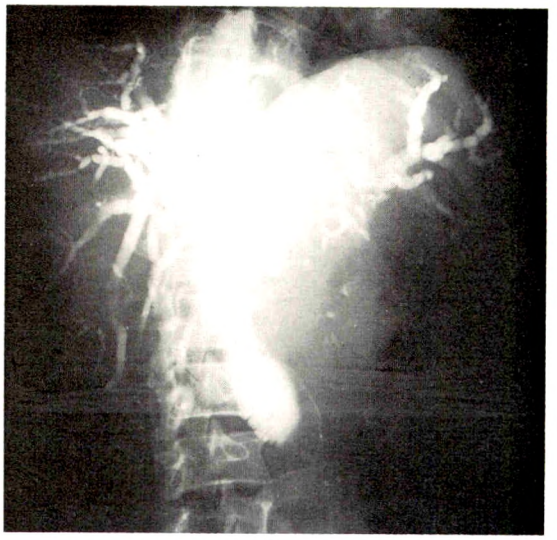


Fig. 9. Carcinoma of the pancreas. There is marked dilatation of the common duct and of the hepatic duct with a convex distal end of the common duct. The gallbladder is markedly dilated. There is nonvisualization of the pancreatic duct. This patient was found to have carcinoma of the head of the pancreas at surgery.

possibly dilatation throughout all divisions. No great distortion of the bile ducts is seen, but the smooth contour generally noted in the normal liver is replaced by mild tortuosity.

There are undoubtedly stages between these two extremes which might present somewhat different findings; however, this has not been so in our series.

It is our feeling that if an attempt at cholangiography is unsuccessful, one must consider strongly the possibility of intrahepatic disease, especially cirrhosis or hepatitis. We feel, as do others,[3] that this presents an opportune time to perform a needle biopsy of the liver and that such a procedure is indicated.

Carcinoma of the Pancreas

The common bile duct may show evidence of obstruction with or without distortion (Fig. 9). The hepatic ducts may or may not be dilated. As described above, we found several cases of multiple liver abscesses in patients with carcinomas producing obstruction of the common bile ducts

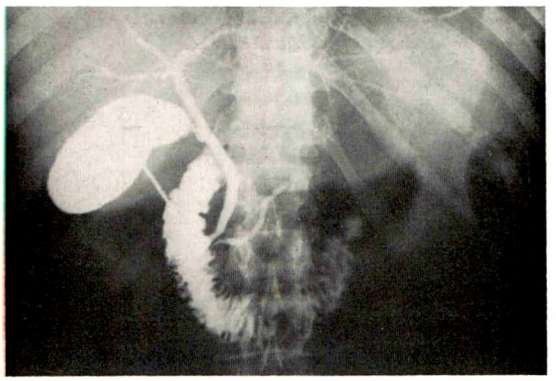


Fig. 10. Carcinoma of the body of the pancreas. There was no evidence of obstruction to the biliary system noted. Reflux into the pancreatic duct was accomplished. Note the rather abrupt halt of visualization of the pancreatic duct. This represented the sight of obstruction by carcinoma of the body of the pancreas.

(Fig. 6). In those cases in which carcinoma of the head of the pancreas is the cause of jaundice, the pancreatic duct does not visualize. We did study one patient who had a carcinoma of the body of the pancreas in whom the pancreatic duct visualized well in part (Fig. 10). There was a rather abrupt halt in the retrograde filling of the pancreatic duct. Such a finding should certainly make one suspicious of either a calculus or tumor in this area of the pancreas.

SUMMARY AND CONCLUSIONS

The technique of percutaneous transhepatic cholangiography is described briefly. The procedure is not complicated, relatively benign and may be very informative.

The diagnostic capabilities are discussed. The test is especially useful in cases of jaundice of unknown etiology. One should be able to differentiate between obstructive and nonobstructive jaundice, as well as to determine the cause of the obstruction in the majority of instances. Roentgenologic findings are present in several of the most common causes of bile duct obstruction which are strongly suggestive of the etiology of the obstruction. The degree of dilatation and tortuosity of the intrahepatic ducts is indicative of the duration and completeness of the obstruction.

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ADENOMYOMA OF THE GALLBLADDER*

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IN A continuing study of benign tumors of the gallbladder, it has become evident that an adenomyoma, when visualized cholecystographically, presents a specific appearance.[7,8] The importance of this precision in diagnosis is that these lesions seem almost invariably to be benign. Specific diagnosis of adenomyoma, therefore, permits conservative management of the patient.

In 14 instances, adenomyoma of the gallbladder has been the diagnosis in resected specimens at Ochsner Foundation Hospital during the past 6 years. In one patient who had not had cholecystography, the cholecystic lesion was discovered at the time of aortic endarterectomy. In another patient, in whom visualization of the gallbladder had been obscured by intestinal shadows, the tumor was encountered during partial colectomy for carcinoma of the colon. In 4 patients with gallstones and varying degrees of cholecystitis, cholecystographic study did not reveal the presence of an associated adenomyoma. In the remaining 8 patients the cholecystographic observations were similar and can be explained by the morphologic nature of the lesion. Consequently, one is tempted to believe that the cholecystographic appearance is diagnostic when present.

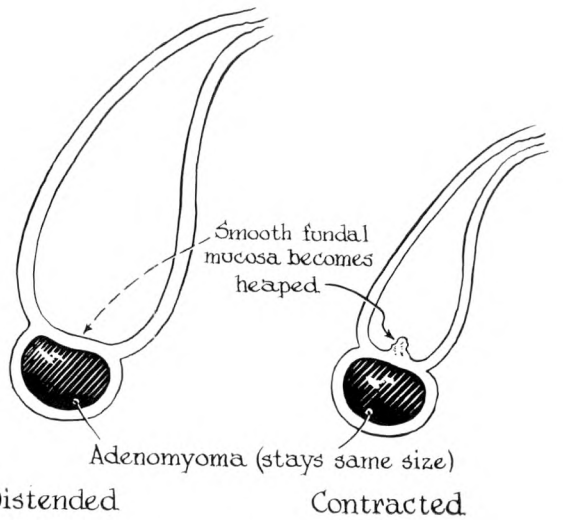


FIG. 1. Diagrammatic sketch of gallbladder in distended (left) and contracted (right) phases showing effect of adenomyoma on mucosa at fundus.

PATHOLOGIC CONSIDERATIONS

Whether adenomyoma of the gallbladder is a true neoplasm is debatable. By some authorities[4] it is considered the most frequent benign tumor of the gallbladder. Others consider it a hamartoma, that is, a developmental anomaly in which normal tissues are present in abnormal location or in abnormal amounts. Jones and Walker[5] refer to them as myoepithelial anomalies. Whatever their origin, adenomyomas are usually found in the fundus of the gallbladder. This was the location in all our cases.

The typical adenomyoma forms a firm, rubbery mass at the fundal end of the gallbladder. Usually, it is rather smooth in contour. In our series, it ranged from 7 to 20 mm. in diameter. When it is seen, the initial impression is that it is a lymph node attached to the fundus of the gallbladder. When the gallbladder is opened and lying flat, the adenomyoma forms a sessile mass, bulging into the lumen as a firm mound of tissue covered with normal appearing mucosa. The mucosa over it may be dimpled or smooth. The lesion involves also the submucosal and muscular elements of the wall of the gallbladder.

On cut surface, a pattern of minute cystic spaces is seen. Microscopically, these are cystically dilated, glandular structures with a lining of columnar cells similar to those of

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the mucosa of the gallbladder. Separating these are variable amounts of connective tissue containing vascular structures and interlacing bundles of smooth muscle.[1] In none of our cases were there associated intramural stones or microscopic abscesses as described by Shepard *et al.*[9] Histologically, the tumor is benign—the only recorded case of malignancy, to my knowledge, being that of Eiserth[3] in which an adenocarcinoma was found arising in an adenomyoma.

It should be stressed that the lesion described here is a true adenomyoma. These cases do not include such entities as cholecystitis glandularis proliferans, intramural diverticulosis, Rokitansky-Aschoff sinuses, or some similar conditions described by Jutras *et al.*[6] under "hyperplastic cholecystoses," or by Colquhoun[2] under the term of "adenomyomatosis" of the gallbladder.

Figure 1 is a diagrammatic representation of the relationship of an adenomyoma to a gallbladder in distended and contracted states. In the normally distended gallbladder (Fig. 1, left), as is seen in initial roentgenograms, the mucosa over the lesion is smooth and the adenomyoma may not be evident at all. Occasionally, it may produce some blunting of the usual smoothly contoured curve of the fundus. When the organ is contracted, as on cholecystograms after a fatty meal, the size of the lesion is decreased, whereas the adenomyoma remains the same size. The mucosa over the adenomyoma forms a small heaped-up mound of tissue (Fig. 1, right). It is this mucosal element that produces the small radiolucent shadow in cholecystograms—a shadow characteristically at the fundal tip and much smaller than the adenomyoma.

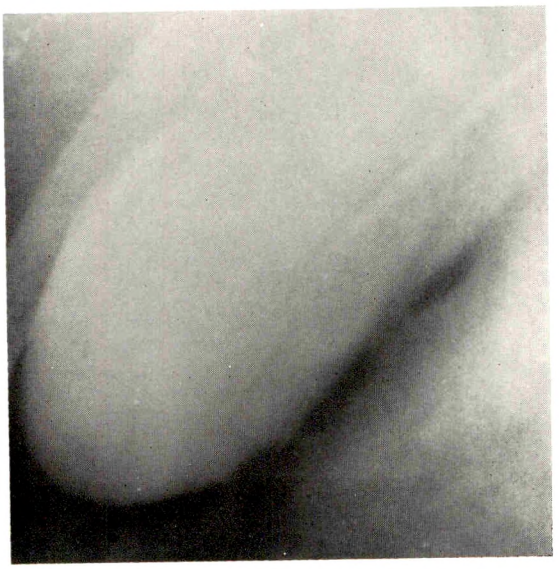


Fig. 2. Cholecystogram of distended gallbladder showing smooth fundus despite presence of adenomyoma.



Fig. 3. Cholecystogram showing a blunted fundal curve in the presence of a large adenomyoma.

CLINICAL OBSERVATIONS

In our 14 patients, the average age was 58 years, with a range from 36 to 77 years. Thirteen were women. Indigestion of some degree was present in 13, and 8 complained of epigastric or right subcostal pain. Five patients had gallstones, and 12 had histologic evidence of some degree of cholecystitis.

ROENTGENOGRAPHIC FINDINGS

Cholecystographic visualization of adenomyoma of the gallbladder is usually good.



Fig. 4. Laminagram of distended gallbladder revealing indentation of eccentrically located adenomyoma.

In 11 of 13 patients examined, the gallbladder was well visualized.

On cholecystograms of the distended gallbladder, the organ usually was of normal size and had a smooth fundus (Fig. 2). In one patient the fundus was blunted and did not have the usual fully rounded contour (Fig. 3). This cholecystographic appearance has been described by others.[5] If the adenomyoma is located eccentrically at the fundus, or if the side of the fundus is pressed against it by the pressure of adjacent organs, a smooth indentation of the side of the fundus may be observed. This occurred in one of our patients, and the defect was best demonstrated on laminagrams of the gallbladder (Fig. 4). We rarely use laminagraphy in cholecystography, but in unusual circumstances it may be helpful.

After the gallbladder has contracted in response to a fatty meal, a characteristic shadow is seen in many cases of adenomyoma. It is a small radiolucent filling defect at the tip of the fundus, usually 1 to 3 mm. in diameter, with or without slight blunting of the fundal contour. It occupies a fixed position and should be readily distinguishable from a gallstone. The type of defect shown in Figure 5 was seen in 5 of our patients. In Figure 6 is shown a variation which was present in another patient, the defect being more obvious because of the relatively small gallbladder after contraction. The radiolucent cholecystographic shadow is usually much smaller than the gross tumor, as illustrated in Figure 7, which is a photograph of a resected gallbladder, the same as the one visualized in Figures 2 and 5.

The original cholecystographic interpretations are listed in Table 1. Gallstones were present in 5 cases, and they usually obscured the associated adenomyoma, or resulted in it being overlooked. In none of the patients in this series with gallstones was the lesion recognized preoperatively. In 2 of these, an abnormality was noticeable in retrospect. In another patient the gallbladder contained several cholesterol polyps, which appeared as small, scattered, radiolucent shadows. If a gallbladder ap-

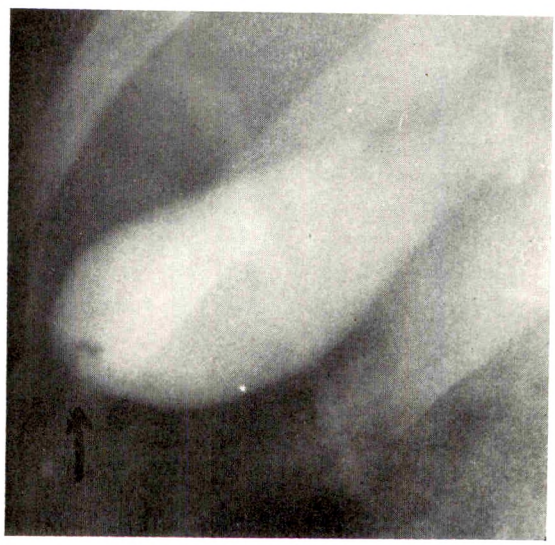


Fig. 5. Cholecystogram of contracted gallbladder in which small fundal defect is now apparent. (Same case as in Fig. 2.)

pears normal in the distended phase but in the contracted phase shows a small, fixed radiolucent area at the fundal tip, a definite diagnosis of adenomyoma of the gallbladder is believed justified.

DISCUSSION

These 14 cases of adenomyoma of the gallbladder represent 27 per cent of the total cases of proved benign tumors encountered during a period of 14 years at the Ochsner Clinic. All were diagnosed within the past 6 years, during which this specific study was underway. It seems unlikely that the incidence is actually increasing. The more frequent recognition is attributed rather to better visualization of the gallbladder by modern methods of cholecystography, to active roentgenologic interest in all gallbladder studies in which small radiolucent defects are demonstrated, and to increasing participation by surgeons and pathologists in the occasional cholecystographic problems of patients who have something other than "another case of gallstones." As the study by Jutras *et al.*[6] beautifully demonstrated, careful handling by surgeons and precise study by pathologists are important if complete information about the abnormal gallbladder is to be obtained.



Fig. 6. Fundal defect is more apparent in cholecystogram when contraction of gallbladder is more pronounced.



Fig. 7. Photograph of resected opened gallbladder showing the relatively large adenomyoma at the fundus. (Same case as in Fig. 2 and 5.)

SUMMARY

Modern methods of cholecystography permit visualization of lesions arising in the wall of the gallbladder in some cases. Adenomyoma of the gallbladder is one of these conditions. Considered to be a benign tumor, it seems to have almost no malignant potential. When it is demonstrated cholecystographically, the findings seem

Table I

CHOLECYSTOGRAPHIC DIAGNOSIS IN 14 CASES OF ADENOMYOMA OF GALLBLADDER

Diagnosis	No. of Cases
Mucosal lesion	6
Gallstones (fundal lesions overlooked-2)	5
Lesions obscured by intestinal gas	1
No visualization	1
No cholecystography	1

characteristic: the distended gallbladder appears normal or occasionally shows slight blunting of the fundal contour and the contracted gallbladder shows a small radiolucent area at the tip of the fundus. When this specific appearance is seen, conservative treatment is justified.

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PAPILLOMAS OF THE GALLBLADDER*

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THE term "papilloma" has been commonly applied to any small radiolucent filling defect attached to the gallbladder wall as visualized on a cholecystogram. Of the various lesions comprising the group of papillomata only the "true papilloma" has assumed clinical importance. This distinction results from a report by Tabah and McNeer[21] in 1953 in which carcinoma *in situ* within 3 of 4 papilloma specimens was described. Hence the question of the malignant potential of such lesions has become of great practical importance in the management of these patients. The clinician, influenced by this and one subsequent report,[15] has generally adopted cholecystectomy as the treatment of choice.

It is our purpose to discuss the various papillomata that may be found in the gallbladder and the related problem of malignant metaplasia. In reviewing this problem we hope to improve roentgen diagnosis and intensify clinical and pathologic interest. We shall also suggest a rational approach to the clinical management of these lesions.

CLASSIFICATION

Protruding lesions of the gallbladder are usually reported by the pathologist simply as "papilloma" or "polyp." These are ambiguous terms which only serve to confuse and should be discontinued in favor of a more precise diagnosis based upon the histopathology encountered. Generally, 4 major types of papilloma can be recognized.

The most common type is the *cholesterol polyp* (Fig. 1, *A*, *B* and *C*). These are firm, smooth nodules, 2 to 6 mm. in size, composed of lipid-laden macrophages or "foam cells" covered by a normal layer of columnar epithelium. They do not constitute new growths but rather a localized collection of cholesterol adherent to the gallbladder wall. They may occur as single or multiple discrete polypoid lesions or in the diffuse form of cholesterolosis, referred to as the "strawberry" gallbladder (Fig. 2, *A* and *B*). Occasionally, the attachments of these fatty polyps become fragile and spontaneous detachment occurs, providing the nidus for stone formation. This may account for the finding of stones and polyps concomitantly within these gallbladders.[22]

The so-called *myoepithelial anomaly*[7] (Fig. 3 and 4) pertains to a thickening of the gallbladder wall involving all layers of the fundus. It is believed to represent a congenital anomaly, and has been named adenoma or adenomyoma which term emphasizes hyperplasia of glandular elements. Characteristically, this is a sessile lesion having a shallow central umbilication and is commonly associated with tiny intramural diverticulosis.

The *true papilloma* (Fig. 5, *A*, *B* and *C*) is a relatively rare lesion found in less than 1 per cent of cases having cholecystectomies. It is a benign neoplasm of a soft, velvety consistency which may be either sessile or pedunculated. These lesions may occur as solitary or multiple growths and range in size from 3 to 8 mm. The papilloma consists of a vascular connective tissue stalk with delicate branching stroma, all of which is covered by a single layer of uniform columnar epithelium.

The *inflammatory polyp* is an extremely rare lesion of the gallbladder. It is a discrete papillary lesion showing inflammatory changes and is found only in association with severe colecystitis. Since the gallbladder is not visualized roentgenographically in this state, the polyp usually is first observed in the surgical specimen.

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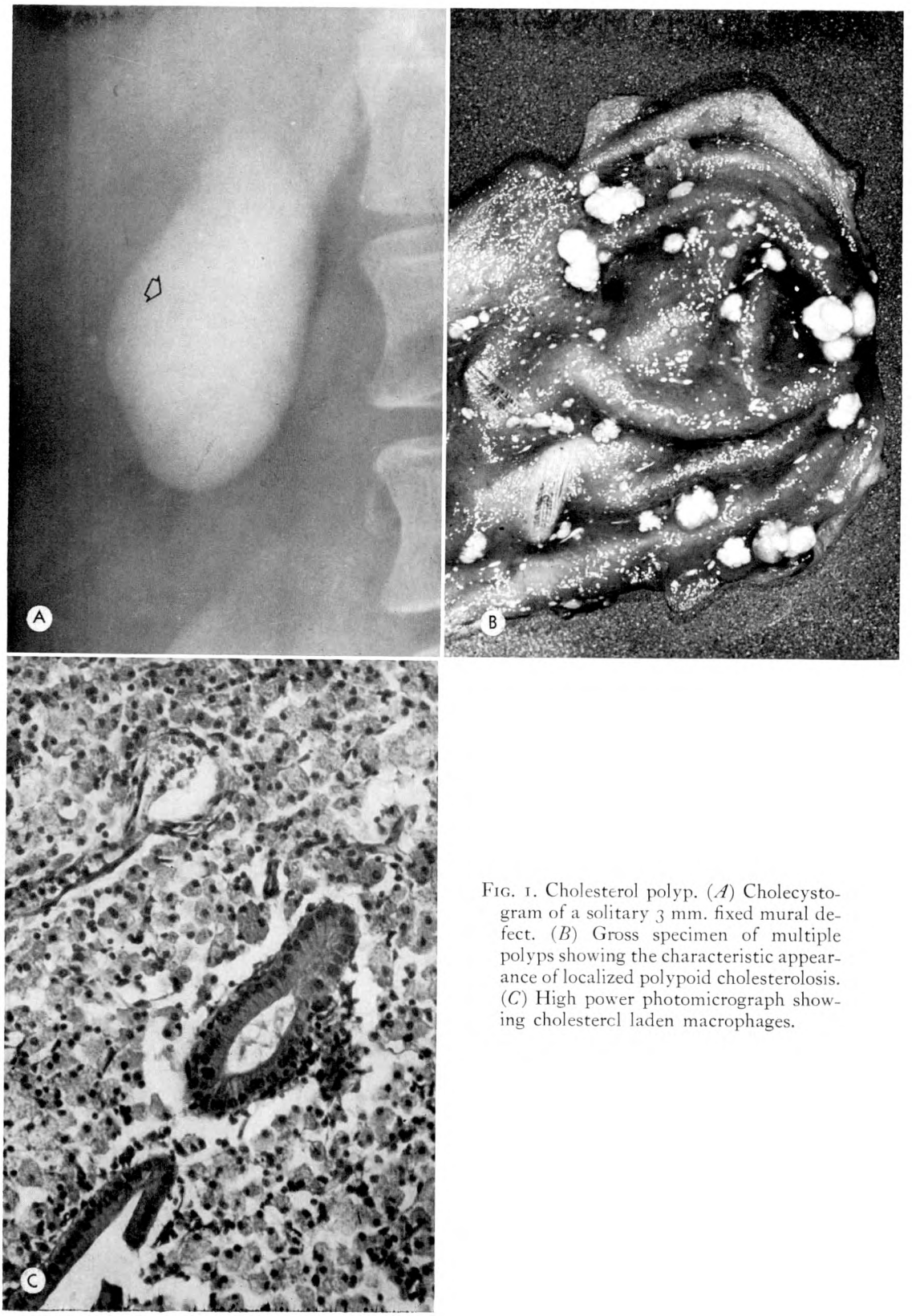


Fig. 1. Cholesterol polyp. (*A*) Cholecystogram of a solitary 3 mm. fixed mural defect. (*B*) Gross specimen of multiple polyps showing the characteristic appearance of localized polypoid cholesterolosis. (*C*) High power photomicrograph showing cholesterol laden macrophages.

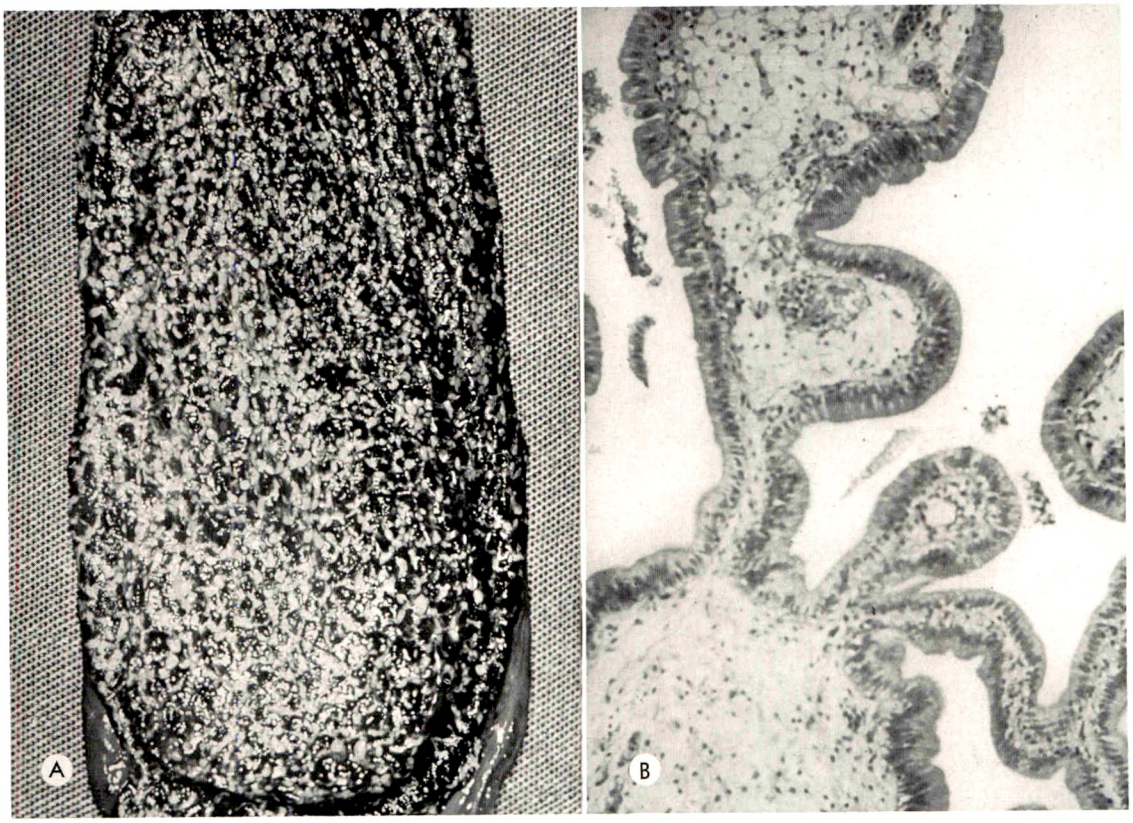


Fig. 2. Diffuse cholesterolosis. (*A*) Photograph of gross specimen showing the diffuse type of cholesterolosis also known as the "strawberry gallbladder." (*B*) High power photomicrograph showing the proliferative villous folds with cholesterol laden macrophages.

ROENTGEN TECHNIQUE

The detection of small intraluminal filling defects by cholecystography depends upon precise roentgenographic technique as well as upon critical evaluation of the image by the roentgenologist. Attention to fundamental details of technique, more than any other single factor, results in a sharp delineation of the gallbladder image and consequently in a higher incidence of identification of tiny gallbladder wall lesions such as polyps, fundic anomalies, Aschoff-Rokitansky sinuses, etc.

Contrast Density. Adequate density or concentration of the contrast medium in the gallbladder can be obtained with use of either oral telepaque (iopanoic acid) or orabilex (bunamiodyl). The intravenous medium (cholografin) is considered less satisfactory than the more dense oral cholopaques.

Penetration. Kilovoltage and milliampere-second settings are important considerations in obtaining optimal penetration of the opacified gallbladder. A low kv. range, around 60 (utilizing the characteristic absorption of iodine), may provide the maximum density in visualization of a faint gallbladder shadow. It may also obscure small defects within a dense gallbladder shadow. Increasing the kilovoltage accordingly will increase penetration of the shadow and make small defects more conspicuous. Care must be taken, however, not to increase the kilovoltage to a point at which densities in the gallbladder become completely gray and flat. This, of course, must be individualized with respect to the thickness of the individual patient and the density of the opacified gallbladder.

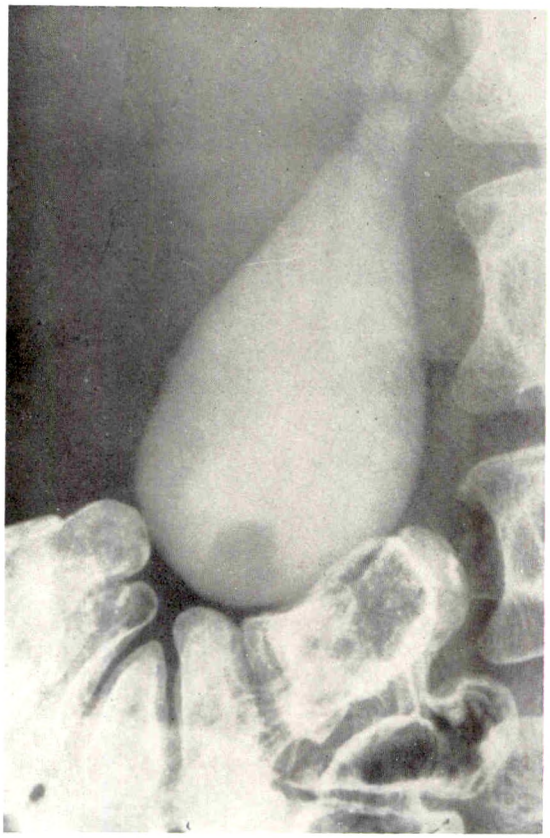


FIG. 3. Myoepithelial anomaly (adenomyoma). Cholecystogram showing a large round 1 cm. lesion of the fundic wall.

Scatter. At too high a kilovoltage, the efficiency of the grid to "clean up" secondary radiation or scatter may be exceeded and results in an unsharp gray image. In addition to the use of an efficient grid, further elimination of secondary radiation can be achieved with the use of cones or small collimating devices.

Motion. A sharper image can be obtained by careful attention to complete cessation of respiration during the exposure and a suitably short exposure time. Plastic sponge wedges and supports should be utilized whenever necessary to maintain an awkward position and to prevent any movements.

Projections. A sufficient number of roentgenograms should be taken in varying projections so as to localize any lesion within the gallbladder, and to eliminate superimposed extraneous shadows such as gas in duodenum, small bowel or colon as well as costal cartilage calcification. It is very useful to employ compression spot roentgenograms with fluoroscopy in order to displace overlying gas, but rarely is the overlying gas so troublesome as to require barium opacification of the gastrointestinal tract. The compression cone has an additional advantage in sharpening the image of the radiolucent lesion and spotting it in a favorable tangential position. Immediate "wet reading" of all roentgenograms is desirable and essential before any additional and more specific views are obtained.

Gallstones must be distinguished from fixed, gallbladder wall lesions. Since most gallstones are freely movable, a comparison of roentgenograms made in prone, erect and decubitus positions will demonstrate their mobility. The right lateral decubitus projection is the most efficient in demonstrating a "layering effect." A suitable period

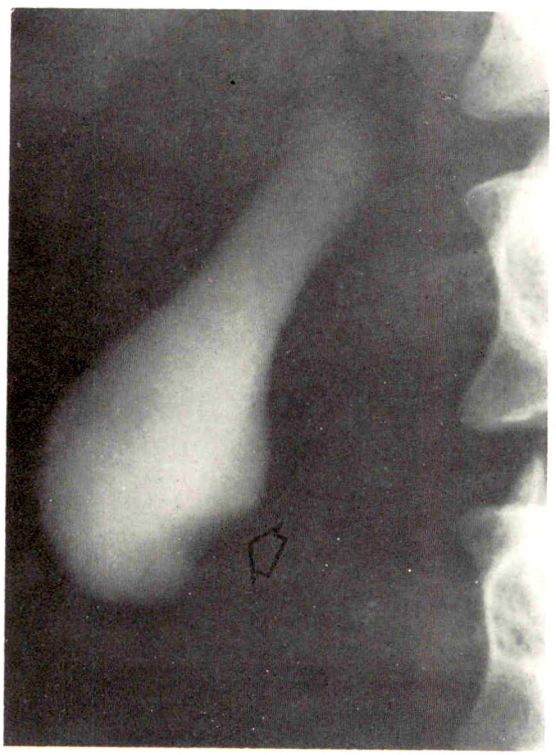


FIG. 4. Myoepithelial anomaly (adenomyoma). Cholecystogram showing shallow filling duct along medial wall of the fundus.

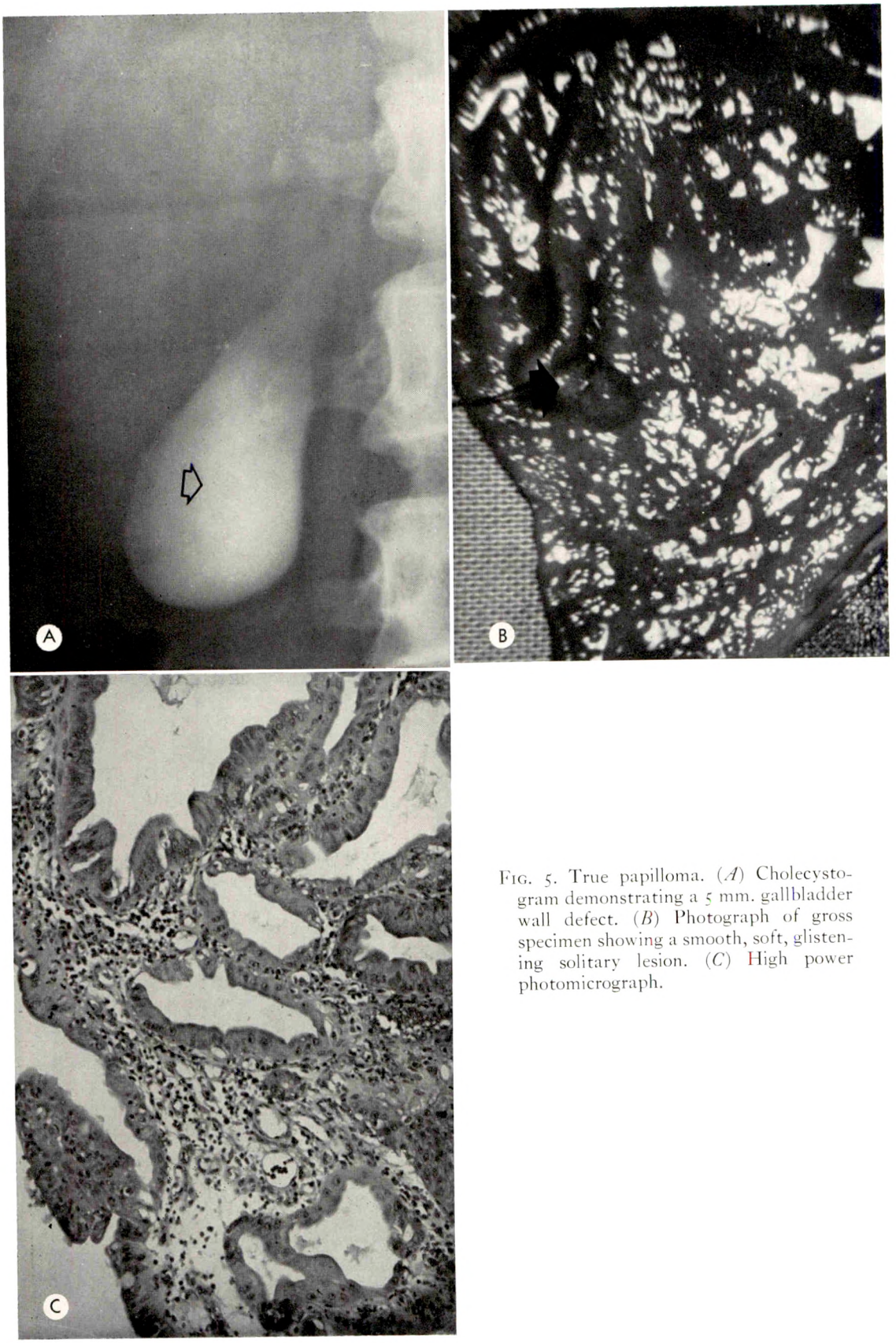


FIG. 5. True papilloma. (*A*) Cholecystogram demonstrating a 5 mm. gallbladder wall defect. (*B*) Photograph of gross specimen showing a smooth, soft, glistening solitary lesion. (*C*) High power photomicrograph.

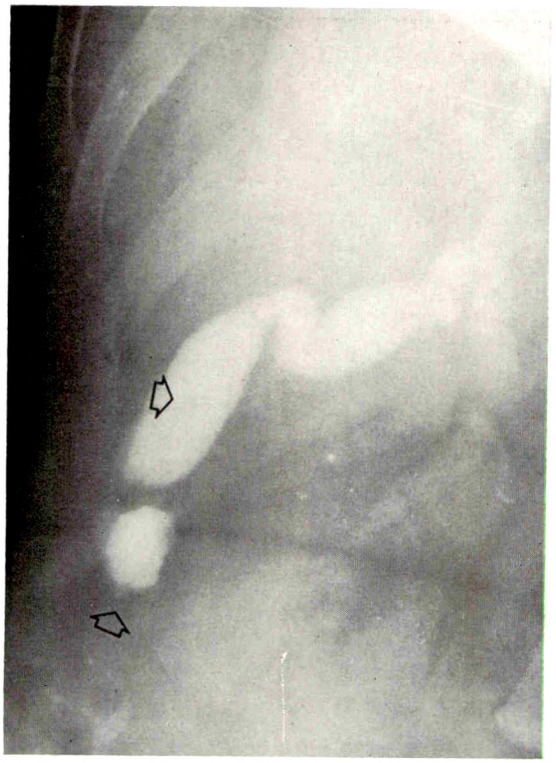


Fig. 6. Cholesterol polyp. Cholecystogram showing a solitary cholesterol polyp in the mid-portion of the gallbladder. In addition there are Aschoff-Rokitansky sinuses in the segmented fundus.

of time must elapse to allow the calculi to settle in the bile. Calculi of higher specific gravity than the bile fluid settle out in a dependent position; calculi of lower specific gravity will float or layer out on the denser bile fluid. In one of our cases the gallbladder contained both a papilloma and a small calculus adherent to the gallbladder wall.

Effect of Cholagogues. Roentgenograms taken following administration of a fatty meal show contraction of the gallbladder and reduction in its volume. This technique most often aids visualization of the tiny mural lesion and reveals some information concerning its mural attachment. Less often a tiny filling defect may become obscured in the contracted gallbladder. Generally, cholagogues provide an over-all advantage.

DIFFERENTIAL DIAGNOSIS

There are a few, reliable distinguishing features to aid in differentiating between the various radiolucent lesions of the gallbladder. Of all the papillomatous lesions, the myoepithelial anomaly has the most characteristic roentgen appearance with its location at the tip of the gallbladder fundus and its central umbilication. It is larger and flatter than the other polypoid lesions and may be associated with small intramural diverticula (Aschoff-Rokitansky sinuses).

Cholesterol polyps are frequently multiple even though only one may be seen on the roentgenogram. These range in size from 2 to 6 mm. in diameter and are adherent to the gallbladder wall. Their fixed position may be confirmed by erect, decubitus and compression spot roentgenograms. Adding to the difficulty in the detection of these filling defects is the fact that these cholesterol polyps may coexist with small calculi. The majority of cholesterol polyps were not found to be associated with stones, but approximately half of our cases showed evidence of chronic cholecystitis; 3 of these cases showed advanced Aschoff-Rokitansky sinuses (Fig. 6). These sinuses or intramural diverticula have been described in association with chronic cholecystitis, cholesterolosis and myoepithelial anomalies.[8,12] Their pathogenesis is confused inasmuch as they are found together with inflammatory disease, degenerative disease and also congenital anomalies, respectively. These sinuses have not been demonstrated in association with the rare papilloma and so it may be considered a point in the differential diagnosis whenever these two coexist.

The true papillomas, while usually single, may occur as multiple growths. On cholecystograms they vary from 3 to 8 mm. in size and may occur anywhere within the gallbladder. In our experience there are no characteristic features to distinguish the true papillomas from other polypoid lesions. Stones or chronic inflammation may or may not be present with these lesions but no direct relationship is known to exist.

The majority of the cases we reviewed were symptomatic. Complaints suggestive of biliary disease were found in approximately two-thirds of those patients operated

upon. Gallbladder opacification in these cases ranged from moderate to excellent.

In the faintly visualized gallbladder, the small filling defects were difficult to appreciate. In one such case of faint opacification, a true papilloma was found together with multiple calculi. No polyps were subsequently discovered in any nonfunctioning gallbladder. In our series (Table 1) stones were found in less than 10 per cent of cases; 90 per cent of the patients were female. Seventy per cent of the patients were over 50 years of age. In most instances a prompt response to fatty meal stimulation was obtained. Sharper delineation of the lesion was observed following contraction of the gallbladder and partial evacuation of contrast medium. In 3 cases that were not operated upon, serial roentgenograms revealed no apparent change in either size or appearance of the lesion or in gallbladder function. One case, followed with serial cholecystograms, showed a growth of the lesion twice its initial size (from 2.5 mm. to 5 mm.) in a period of 4 months. The surgical specimen disclosed a firmly attached cholesterol stone.

In summation, the roentgen differential diagnosis depends upon very few specific findings such as an umbilicated fundic defect, multiplicity of polyps or presence of Aschoff-Rokitansky sinuses. For the most part these lesions are almost impossible to differentiate.

TABLE I

CASE MATERIAL

	No. of Cases	Incidence (per cent)
Papilloma diagnosed roentgenographically	32	
No. of these patients operated upon	20	
Cholesterol Polyps	11	55
Myoepithelial Anomaly	2	10
True Papillomas*	5	25
(a) 3 with stones		
(b) 4 with chronic cholecystitis		
False Positive Diagnoses	2	10
Total	20	100

* In one patient 3 discrete papillomas were found unassociated with either stones or inflammation.

DISCUSSION

In reviewing the literature, one is impressed with the wide disagreement among authors in respect to the incidence of true papilloma of the gallbladder. This results from the loose application of the term "papilloma" to any polypoid tumor. Radiologists, clinicians and even pathologists fail to distinguish the rare neoplastic benign growth from the relatively more common cholesterol polyp. As a result of confused nomenclature, such early writers on the subject as Kirklin[11] and Phillips[16] reported a high incidence of these lesions: 8.5 per cent in 17,000 cases having cholecystectomies at the Mayo Clinic. In 1935, Kerr and Lendrum[9] reviewed the literature and were the first to distinguish the various lesions comprising this nondescript group. They accepted only 7 cases of true papilloma by their rigid criteria.

Kane *et al.*[10] reported an incidence of 0.4 per cent in 2,000 surgical specimens. Gagliardi and Gelbach[5] cited 1 case in 292 cholecystectomy patients. Shepard *et al.*,[17] in reviewing the Mayo Clinic records of 1941, found 1 per cent incidence of papilloma. Swinton and Becker,[20] analyzing 4,553 cases of gallbladder operations at the Lahey Clinic, found only 7 benign tumors (4 papillomas and 3 adenomas). Ten Eyck[22] reported 5 true papillomas in 2,544 patients having cholecystectomies. Tabah and Mc Neer[21] in their extensive bibliography tabulated 81 papillomas reported up to 1953.

In the interest of clarity, the term "papilloma" should be restricted to those lesions which are truly neoplastic and arise from a vascular connective tissue stalk with normal epithelial covering.

By far, the great majority of fixed filling defects seen roentgenographically are cholesterol polyps, as recently shown by Myhre,[14] who found 30 such lesions on roentgenograms; of the 8 patients who were operated on, 7 had cholesterol polyps and 1 had a gallstone.

The relationship of papilloma to cancer of the gallbladder remains controversial. Halpert[6] believes that no such relationship exists. However, other authors[8,9,23] besides Tabah and McNeer[21] have reported malignant changes in papillomas; Wellbrock[23] observed malignancy in 2 out of 69 adenomas. Arminski[1] found 3 cases reported in the European literature. Ochsner and Carrera[15] described 1 carcinoma *in situ* in a group of 10 polypoid tumors.

It is notable that all of the reported cases of malignant "papilloma" have been instances of *in situ* carcinoma. No single case of invasive carcinoma has been found. In our series no evidence of malignant changes was noted. It is known that the diagnosis of *in situ* carcinoma is often subject to individual interpretation; chronic inflammation may play a role in this interpretation. Moreover, the general theory of malignant degeneration within mucosal polyps, until now undisputed, has been recently challenged.[4,13,18,19]

While the case for premalignancy was best presented by Tabah and McNeer, the evidence accumulated in more recent reports has not supported this contention. To our knowledge, no one has shown invasive carcinoma existing in a papilloma in either a surgical or autopsy specimen. Only with critical studies of all papillomatous tumors of the gallbladder in surgical and autopsy specimens together with long term follow-up of the nonoperated cases, will this controversial question be answered.

MANAGEMENT

The patient with symptoms of biliary colic combined with a mural defect should present no problem in management. With cholecystectomy the gallbladder wall lesion and any occult stones which may be present are simultaneously removed. In our series, 3 out of 5 patients with papilloma had associated stones (Table 1).

When in the presence of these lesions there are no associated calculi or symptoms, the surgeon may feel justified in performing an operative procedure if he believes these lesions to be premalignant. Furthermore, he may operate on the basis that the lesion might be a cholesterol polyp which would be evidence of a pathologic gallbladder.[8,15]

On the other hand, there are cogent reasons for not operating upon such patients. For one, there is a paucity of evidence supporting the contention that malignant metaplasia occurs in gallbladder papilloma. Surprisingly few cases have been reported substantiating the initial report (1953) and no cases of invasive carcinoma have been described. Furthermore, the papilloma is a rare lesion with an incidence of less than 0.5 per cent of cholecystectomy cases.[5,10,20] Thus, recognizing the extreme rarity of *in situ* carcinoma occurring in a true papilloma one could only conclude that the combination of these rare occurrences is indeed statistically very remote.

If there were no mortality involved in gallbladder surgery, then prophylactic cholecystectomy with the salvage of even a small number of patients would be rewarding. However, with a surgical mortality risk approaching 1 per cent in all cholecystectomy cases and higher in elderly patients, the hazards of surgery outweigh any advantage that might be anticipated.

In the final analysis the course of management must be individualized for each patient, giving due consideration, among other things, to surgical risk, pertinent symptoms and emotional status in any decision to operate. When a decision not to operate is chosen, periodic roentgen and clinical observations are indicated. Any change in roentgen appearance or in the clinical picture would warrant reconsideration of surgery. At present we feel that careful observation of the asymptomatic patient is justified.

SUMMARY

1. Radiolucent defects within the opacified gallbladder may be produced by any one of the following: (a) gallstone, (b) cholesterol polyp, (c) myoepithelial anomaly, or (d) true papilloma.

2. Radiolucent gallstones can be easily differentiated from other mural lesions by appropriate roentgen techniques.

3. Myoepithelial anomalies may be differentiated also by their characteristic roentgen features.

4. Cholesterol polyps account for the great majority of noncalculous radiolucent filling defects in the gallbladder.

5. While true papillomas are rare, their importance has become magnified by the reported incidence of carcinoma *in situ*.

6. In our 5 cases of true papilloma, no histologic evidence of carcinomatous change was found.

7. Review of the literature fails to reveal sufficient evidence to support the theory that malignant metaplasia occurs.

8. At present we have adopted a conservative approach in the management of these papillomatous lesions, favoring cholecystectomy for the symptomatic patient and relying upon serial cholecystography and clinical observation for the remainder.

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A PRELIMINARY CLINICAL EVALUATION OF A NEW CHOLECYSTOGRAPHIC MEDIUM, BILOPAQUE*

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BILOPAQUE,* sodium 2-(3-butyramido-2,4,6-triiodobenzyl) butanoate, is a result of the continuing search for more effective cholecystographic media. It is a derivative of telepaque† and differs from it chiefly in the butyrylation of the amine group. Telepaque is insoluble in water while bilopaque as a sodium salt of iopanoic acid is soluble in water. Holmdahl and Lodin[5] have noted a significant increase in blood levels in patients receiving the sodium salt of iopanoic acid over those who received iopanoic acid in its usual form. Bilopaque contains 57.4 per cent iodine while telepaque contains 67 per cent iodine. Excretion of the bilopaque is through the urinary and digestive tracts in approximately equal amounts.

Preliminary tests of this new contrast agent in the cat, dog, and monkey showed it to be an effective cholecystographic agent in these animals. With dosages up to 20 times the maximum anticipated human dosage, no untoward effects were demonstrated in animal studies.[10] Bilopaque was supplied for this preliminary clinical trial in 750 mg. capsules with the usual dose of 6 capsules representing 4.5 gm.

METHOD OF STUDY

One hundred consecutive in-patients for whom cholecystography had been ordered were given bilopaque as the cholecystographic agent. The initial dose was 4.5 gm. but, in inconclusive studies, the patient usually had a repeat examination and 9 gm. of the material was administered; 2 patients received a third examination. There were thus 114 examinations with bilopaque in the 100 patients. As 2 other cholecystographic agents, orabilex‡ and telepaque, had been used extensively in this department, 100 patients from each of these groups were selected to be compared with the bilopaque group in a triple blind study in order to evaluate the degree of gallbladder opacification, visualization of the duct system, cholelithiasis, and residual contrast in the bowel. Repeat examinations in these two groups of patients similar to those in the bilopaque group were also evaluated so that there were 123 examinations with orabilex and 127 examinations with telepaque. The initial orabilex dose was 4.5 gm. with 9 gm. being used in the repeat examinations; the initial dose of telepaque was 3 gm. with 6 gm. being given in the repeat studies.

All of the above studies, 364 in number, were removed from their permanent storage folders, the date and case numbers were masked off, and they were placed in coded identical temporary film jackets by clerical help. The 3 series were thoroughly shuffled and read in a completely random manner by two examiners who had no idea which of the media was used in any of the studies being examined. The roentgenographic evaluation, therefore, represented a triple blind study of the 3 media in question.

After all of the examinations had been evaluated, the roentgenograms were identified with the agent used and the results were tabulated. Visualization of the gallbladder was graded excellent, good, fair, poor, and nonvisualization. Either "excellent" or "good" meant that the studies

* Bilopaque (brand of sodium tyropanoate) supplied by Winthrop Laboratories, New York, N. Y.

† Telepaque (iopanoic acid), Winthrop Laboratories.

‡ Orabilex (bunamiodyl), E. Fougera & Co., Hicksville, N. Y.

* From the Department of Radiology, Blodgett Memorial Hospital, Grand Rapids, Michigan.

Table I

A COMPARISON OF THE VISUALIZATION OBTAINED WITH ORABILEX, TELEPAQUE AND BILOPAQUE

Degree of Visualization	Orabilex (4.5 gm.) (per cent of 123 studies)	Telepaque (3.0 gm.) (per cent of 127 studies)	Bilopaque (4.5 gm.) (per cent of 114 studies)
Excellent	21.9	31.5	34.2
Good	29.2	25.9	27.2
Combined Excellent and Good	51.1	57.4	61.4
Fair	19.5	10.2	11.4
Poor	12.2	14.9	7.9
None	17.0	17.3	19.3
Calculi	14.6	15.4	13.1
Duct Visualization			
None	60.1	62.2	69.3
+	31.7	28.3	21.9
++	8.1	9.4	8.8
Per Cent Visualized	39.8	37.7	30.7

were of sufficient quality to be completely diagnostic while the other gradings indicated that a greater degree of opacification was desired.

The ducts were graded from 0 to 2+, with 1+ indicating equivocal or faint visualization, while a 2+ indicated that the duct was sufficiently opacified to be of diagnostic significance. The presence or absence of cholelithiasis was also noted. The bowel residual was graded none, minimal, or moderate to heavy. Any examination preceded within 2 days by a barium study was eliminated from this evaluation in order to avoid any possible confusion due to the barium.

The side effects of bilopaque were evaluated by interviews with each patient the morning after the contrast material had been given. Any symptom noted after the ingestion of the cholecystographic medium was recorded so as to obtain an "absolute" incidence of side effects, but an attempt was also made to distinguish between the side effects directly related to the cholecystographic agent and similar symptoms present prior to the ingestion of the bilopaque. An "equivocal" side effect was recorded for any symptom that was consistent with previous symptomatology and when the patient stated in response to a direct question that the symptom or symptoms did not appear to be due to or to be worse after the ingestion of the cholecystographic agent. A brief history of allergy or drug idiosyncrasy was also recorded.

No special preparation was given to the patients other than a fat-free supper the night prior to roentgenography. Routine cholecystography was performed approximately 18 hours after the ingestion of the contrast material. The roentgenographic technique was identical for the 3 series of examinations.

RESULTS

VISUALIZATION

The results (Table 1) showed that all 3 media produced excellent or good densities in more than one-half of the studies. Bilopaque studies received the best over-all evaluation with 61.4 per cent of these being rated excellent or good while 57.4 per cent of the telepaque studies and 51.1 per cent of the orabilex studies were thus rated. Poor visualization was noted least often in the bilopaque studies (7.9 per cent) and

TABLE II

A COMPARISON OF THE RESIDUAL CONTRAST IN THE COLON WITH ORABILEX, TELEPAQUE AND BILOPAQUE

Degree of Residual	Orabilex (4.5 gm.) (per cent of 93 studies)	Telepaque (3.0 gm.) (per cent of 120 studies)	Bilopaque (4.5 gm.) (per cent of 87 studies)
None	43.0	34.1	52.8
Trace	35.4	49.1	41.3
Moderate to Heavy	21.5	16.6	5.7

most often when telepaque was used (14.9 per cent).

The percentage of studies showing duct visualization was highest in the orabilex group with some degree of opacification seen in 39.8 per cent of the examinations. The duct was visualized in 37.7 per cent of the telepaque studies and in 30.7 per cent of the bilopaque group. The 2+ degree of opacity of the ducts, however, was more uniform, with 8.1 per cent of the orabilex, 9.4 per cent of the telepaque and 8.8 per cent of the bilopaque examinations showing such opacification. No attempt was made to determine the number of duct visualizations which followed the fatty meal.

Cholelithiasis, as would be expected in similar groups of patients, was rather a constant finding in the 3 series. It was noted in 14.6 per cent of the orabilex group, 15.4 per cent when telepaque was used, and in 13.1 per cent of the bilopaque studies.

The bowel residual evaluations are tabulated in Table II. The bilopaque group showed a significantly lower percentage of moderate to heavy colonic residue (5.7 per cent) than either of the other groups. There was no visualized bowel residue in 52.8 per cent of the bilopaque examinations and this percentage was higher than that of either of the other two series. The telepaque studies showed the highest incidence of a trace of bowel residual at 49.1 per cent.

SIDE EFFECTS

Cholecystographic media are not entirely innocuous. The vast majority of side effects is more troublesome to the patient than dangerous but occasionally more severe untoward reactions, particularly in the urinary tract, are noted.[1,4,8] The side effects in our bilopaque series are compared to several other reported series[2,3,6,7,9] using telepaque and orabilex in Table III. These series were selected chiefly because the dosage of these media was comparable to that of the bilopaque, 4.5 gm. for the orabilex and 3 gm. for the telepaque series. Of the 114 bilopaque examinations, in 80.7 per cent there were no side effects. All signs and symptoms are recorded, but only 16 of the 28 side effects listed were determined to

TABLE III

A COMPARISON OF SIDE EFFECTS WITH REPORTED SERIES

Authors	Orabilex (4.5 gm.)				Telepaque (3.0 gm.)				Bilopaque (4.5 gm.)		
	Cornelius *et al.*[2] (per cent of 150)	Meszaros and Rich[6] (per cent of 500)	Morgan and Parks[7] (per cent of 92)	Average (per cent of 742)	Whitehouse and Martin[9] (per cent of 500)	Dunne *et al.*[3] (per cent of 116)	Morgan and Parks[7] (per cent of 95)	Average (per cent of 711)	Present Series (per cent of 114)		
Side Effects									True	Equivocal	Total
None	64.0	—	—	—	62.5	79.6	—	—	—	—	80.7
Nausea	18.0	14.0	20.6	17.5	5.8	8.6	29.0	14.7	9.6	6.2	15.8
Vomiting	4.0	4.0	3.2	3.7	.5	.0	2.0	.8	.0	2.7	2.7
Diarrhea	2.0	4.0	10.8	5.6	25.3	12.0	40.0	25.7	1.7	.8	2.5
Dysuria	.7	2.0	1.0	1.2	13.7	.8	8.0	7.5	.8	.0	.8
Others	3.3	3.0	33.7	13.3	2.8	—	48.0*	—	1.7	.8	2.5

* Many patients had multiple side effects in this series.

be definitely related to the cholecystographic medium. The remaining 12 complaints were present prior to the ingestion of the bilopaque and did not appear to be increased or caused by the material. These latter are listed as "equivocal" side effects in Table III. Approximately half of the patients with side effects had a history of allergy or drug idiosyncrasy.

Nausea was the most common complaint, being present in 18 instances, and in only 4 cases was it considered severe. Three of the severe cases and 4 mild cases of nausea were classified as "equivocal." Nausea definitely related to the bilopaque was noted in only 9.6 per cent of the total series.

There were only 3 mild cases of vomiting, all of which were regarded as equivocal. Diarrhea of relatively mild nature was recorded 3 times. In 2 instances this was thought to be related to the bilopaque ingestion. One of the 2 patients had received a total of 20 gm. of bilopaque over a 3 day period and had 2 loose stools after the third dose.

There was only one complaint of mild dysuria in the 114 examinations.

Other side effects were rare. Abdominal cramps were recorded in 2 patients, one of whom had presented originally with the same complaint. There was one case of an allergic dermatitis. This patient had no reaction after the initial dose of 4.5 gm. of bilopaque, but approximately 3 hours after ingestion of double dose (9 gm.) she noted the onset of an erythematous burning and pruritic rash over the thighs and lower trunk. This dermatitis subsided within 24 hours without specific treatment.

DISCUSSION

It is obvious that the ideal cholecystographic medium is still not available. In our relatively small series of 364 examinations, all 3 media demonstrated good or excellent diagnostic visualization in more than one-half of the cases. Statistically, bilopaque showed the best gallbladder opacification of the 3 and had significantly lower bowel residue. There was a low incidence of side effects and no serious reactions to bilopaque. Nausea was attributed to bilopaque in only 9.6 per cent of the examinations. Diarrhea and dysuria were almost nonexistent with bilopaque.

Although the number of cases in this preliminary study is small, the findings to date indicate that of the 3 media, bilopaque, in our opinion, is the cholecystographic agent of choice because of its high degree of capability to opacify the gallbladder, the low incidence of side effects, and the relative lack of troublesome bowel residual.

SUMMARY

A clinical trial of a new cholecystographic agent, bilopaque, is reported. The cholecystograms of 100 patients to whom bilopaque was administered were compared to similar groups of 100 patients who received orabilex and telepaque in a triple blind study. The side effects related to the use of bilopaque were recorded and compared to published reports of side effects following orabilex and telepaque. In our series, the best gallbladder visualization, least bowel residual, and fewer reported side effects were noted when bilopaque was used as compared to the other media. With the evidence obtained, we feel that of the 3 media bilopaque is the cholecystographic agent of choice.

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CONSIDERATIONS OF CHOLECYSTOGRAPHIC CONTRAST MEDIA

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THE radiologic literature contains numerous clinical observations that concern themselves with the efficacy of contrast media. The bibliography concerning toxicity and excretory pathways of contrast media is also voluminous. There have been relatively few reports about the underlying physical-chemical phenomena that govern these excretory pathways and toxicity, and the publications on the fate and metabolism of contrast media with reference to their influence on clinical radiology are even less. It is for this reason that an attempt is made to elucidate some aspects of the fate and metabolism of cholecystographic contrast media as they relate to clinical radiology.

In this connection, it should be pointed out that in order to study fruitfully the complex phenomena which occur in living beings, we must first of all lay down principles of experimentation and then apply them to physiology, pathology, and therapeutics.[2]

The architect's dictum that "form follows function" applies equally well to the design and development of cholecystographic contrast media, which begs the question: What are these criteria?

The efficacy of a cholecystographic contrast medium is not only based upon its absorption index but also its route of elimination, its lack of toxicity and interference with laboratory determination of blood, urine, and liver function. Therefore, an ideal cholecystographic contrast medium would have the following properties: (1) 100 per cent absorption; (2) immediate elimination by the hepatic-biliary system; (3) absolute nontoxicity; and (4) lack of interference with laboratory tests.

It is rather doubtful that such an ideal cholecystographic contrast medium could ever be developed as long as it is necessary to utilize iodinated compounds, and the search for an ideal medium is unabated.

How do presently available cholecystographic contrast media compare with the criteria of such an ideal medium and what are the clinical complexities involved?

ABSORPTION INDEX

No one will dispute the statement that the diagnostic reliability of oral cholecystography depends upon the degree of absorption of the contrast medium employed.[9]

The rate and degree of absorption may be judged either by the estimation of the amount of substance remaining in the bowel, or, more precisely and with more reliability, by determining the iodine content or radioactivity of a tagged compound in the blood and bile following administration.

The chemical structure of such an iodinated compound plays a most important role and, therefore, it should have a proper balance between lipophilic and hydrophilic groups to insure absorption from the intestinal tract.[1]

That a change of a chemical structure can play a determining role upon the absorption index of such a compound has been demonstrated by the replacement of iopanoic acid by its sodium salt. The sodium salt of this compound showed an appreciable increase of absorption when checked by the amount of intestinal residue or by the analysis of blood samples for iodine content following its administration.[23] However, the improved absorption of this compound resulted in an increase of its toxicity.

Radioisotope studies with more re-

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cently developed cholecystographic contrast media, such as ipodate sodium and bunamiodyl sodium showed a markedly improved absorption index as demonstrated with ipodate sodium, approximately 70 per cent[7] with bunamiodyl sodium 85 per cent to 90 per cent.[16] The pharmacology of both compounds indicates no increase in the toxic properties.[7,18]

ROUTE OF ELIMINATION

The route of excretion of a contrast medium is a vital factor in the development of these compounds; *i.e.*, a urographic contrast medium must have a predominant urinary elimination and a cholecystographic medium must have a predominant hepatic-biliary elimination.

It was assumed that, perhaps, the molecular weight of such a compound might determine whether a substance goes to the gallbladder or to the kidney. Empirical experience, however, did not support this thesis. A postulation that only relatively weak acids are suitable for cholecystographic media and strong acids for renal contrast agents was also proved to be unreliable. Only experimental experience will decide the preferred route of elimination and the most classic example is the development of cholografin which was prepared with the clear intention of obtaining a urographic contrast medium which proved to be an excellent cholecystographic medium when tested.[13]

A reliable indicator for the efficacy of a cholecystographic medium is the *ratio of the hepatic-biliary elimination versus that of urinary elimination*. The experimental data compiled on the following compounds reveal that efforts to improve cholecystographic media reflect definite progress: the approximate ratio of elimination of iophenoxic acid 1:1.5;[22] iopanoic acid 1.3:1; ipodate sodium 2.1:1; bunamiodyl sodium 3:1.[7,16,19,31] Any underlying hepatic or biliary derangement, however, will alter the ratio. Therefore, the radiologist should have some understanding of the hepatic clearance, which shall be considered at a later point. In parenchymal liver disease, for instance, the decreased number of functioning hepatic cells can take up only a limited amount of the given dose of a medium for conjugation and for elimination. With the advent of readily absorbable cholecystographic contrast media, the clinician should *re-orient his attitude toward dosage* since increasing the dose will not force the process of conjugation and elimination by the liver. Indeed, overdosage might lead to undesirable results since rapidly produced high iodine blood levels may give rise to a clinically significant hypotension. The significance of blood pressure changes following oral and intravenous cholecystography has been recently reported in the literature.[15,24] It would appear, therefore, that the addition of pre- and postcholecystographic blood pressure recording to the patient's work-up might give a forewarning and some insight into potential complications.

TOXICITY

One of the basic steps in the analysis of the pharmacologic properties of a chemical substance is the characterization of the dose-mortality curve in the experimental animal.[12]

The toxicity of a contrast medium is accurately determined by the quantity absorbed by the body. Therefore, the intravenous LD_{50} reflects best the actual toxicity of a given agent. Since there are variations in the toxicity values in different species, the compound should always be screened in different animals, such as the mouse, rat, rabbit, cat, and dog. It appears worthwhile mentioning that the juxtaposition of the oral LD_{50} with the intravenous LD_{50} of a cholecystographic medium permits an assessment of its absorption index.

The aforementioned dose-mortality curve in animals does not guarantee complete safety from an occasional untoward reaction in a subject on the extreme end of the curve. It becomes of paramount importance to discover means of determining such a rare individual who falls into the extreme

lower range of the asymptotic part of the dose-mortality curve.

It is, indeed, essential that there should be a broad margin between the therapeutic dose and the toxic dose.[7,11,18,19]

Untoward reactions that are characteristically allergic (hypersensitivity) have been described with every compound and are generally of an anaphylactoid nature and conditioned by previous exposure and sensitization to the drug or similar compounds. They are mediated by an antigen-antibody reaction.

There are 3 main types of hypersensitivity reaction: (a) serum sickness; (b) anaphylactoid reaction; and (c) alteration in reactivity of certain tissues which results in degenerative changes if the antigen (drug) is again applied.[25]

In the understanding of drug hypersensitivity, it must be recognized that practically every drug is capable of combining with proteins, thus forming an antigenic conjugate.[25] This, again, stimulates the formation of antibodies. Because of the inaccuracy of our present knowledge, it is impossible to correlate the chemical structure of a compound with its potential allergenic response. It also should be kept in mind that *quantity* plays a role in the severity of allergic manifestations. Idiosyncrasy is not an allergic reaction and implies an inherent qualitative abnormal reaction to a drug and stems, in all probability, from a hereditary enzyme deficiency.[25]

INTERFERENCE WITH LABORATORY TESTS

The interference with laboratory tests by the iodinated compounds is closely related to their metabolism and elimination. If we speak of hepatic clearance, we should make a distinction between *metabolic clearance* and *hepato-biliary clearance*. Substances which are metabolized by the polygonal cells of the liver, such as galactose or lactic acid, fall within the category of "metabolic clearance." Substances, such as bilirubin, cholecystographic media, rose bengal, bromsulphalein and others, which are mostly bound to the serum albumin and excreted through the biliary ducts, are subjected to "hepato-biliary clearance."[3,4] The competition for clearance between substances which are excreted by the "hepato-biliary clearance" has been observed for quite some time and has been demonstrated *in vitro* and *in vivo* studies.[8,14,19,29,30]

After simultaneous or successive administration of two or more such substances, the clearance of one of the substances is lowered whereas the other is preferentially excreted. This is specific to "hepato-biliary clearance" and does not exist in "metabolic clearance."[4] It, therefore, should be clearly understood and be expected that bromsulphalein retention or transient hyperbilirubinemia is the result of a *competition for the route of excretion*. The physician should be alerted to the fact that any abnormal findings relative to these liver function tests when carried out simultaneously or successively with the administration of cholecystographic media are due to the preferential elimination by the "hepato-biliary clearance" and not evidence of a pathologic process. The degree of bromsulphalein retention or hyperbilirubinemia is directly related to the quantity of medium excreted by the liver as well as the functional state of the liver and, therefore, in the presence of underlying hepatic derangement, the values obtained are elevated accordingly.

A similar mechanism (transient "occupation" of the hepato-biliary excretion mechanism) is responsible for an increased excretion of coproporphyrin in the urine immediately following the administration of iopanoic acid and bunamiodyl sodium.[6]

The affinity of iodinated compounds to the thyroid, to serum albumin, and what determines the degree of binding is poorly understood and needs further elucidation. Empirically, we know that there is a broad variation in the protein-binding capacity of different cholecystographic media and, therefore, interference with protein bound iodine determination varies by years (iophenoxic acid), months (iopanoic acid), and weeks (bunamiodyl sodium).[20,28]

The time of adherence to the thyroid tissue also varies from one compound to another but as a general rule the time period of interference, as found with protein bound iodine determination, is true for thyroid uptake studies, and thus indicates a link with the protein binding of these substances.

The protein binding of parenteral contrast media has been recently investigated by Lasser *et al.*,[17] and revealed some most intriguing characteristics. The significant conclusions which might be of interest in the content of this paper are as follows:

1. For the triiodobenzoic acid compounds, the presence or absence of a prosthetic group at the 5 position appears to determine the relative weakness, or relative strength of binding with albumin.
2. There is marked species variation in the degree of protein binding for each of the contrast media.
3. The crenation effect in red blood cells may be related to the binding of contrast media to protein in or around the red blood cells.
4. There appears to be a high degree of correlation between the strength of binding determined by equilibrium dialysis in their investigation and published reports of intravenous LD_{50} toxicity expressed in millimols per kilogram dosage levels.
5. The more highly protein bound contrast media appear to be preferentially excreted in the bile and the less highly bound media in the urine.
6. *In vitro* studies of the binding dynamics of bilirubin relative to some of the contrast media suggest that both urokon and cholografin are capable of competitively displacing bilirubin from albumin in the human.[17]

It should be emphasized that their findings were obtained in studies with *parenteral* contrast media and if these findings apply to *oral cholecystographic media*, they are, indeed, subject to further investigation. However, the route of administration (oral versus intravenous) and the different mechanism of absorption will certainly play a role in the final results. It becomes quite obvious that the study of Lasser and his co-workers demonstrates the complexity involved (for instance, toxicity) in the fate and metabolism of contrast media. It clearly shows that there is a virgin field for future research.

PSEUDOALBUMINURIA

From time to time, attention has been focused in the literature on the occurrence of pseudoalbuminuria following the administration of cholecystographic media.[10,21,26,27]

During the past half century, a large number of tests for the detection of protein in the urine has been described. Three of these tests have earned wide acceptance and are now used exclusively in clinical practice. These are the sulfosalicylic acid test, the nitric acid ring test, and the heat and acetic acid test, all of which are known as turbidity tests.

In the interpretation of routine urinalysis, it should be kept in mind that these tests fail to differentiate between pseudoalbuminuria and true proteinuria.

Pseudoalbuminuria (pseudoproteinuria) refers to a *false* positive protein test due to the presence of nonprotein metabolites in the urine. The more common nonprotein metabolites found are those of radiopaque contrast media for gallbladder visualization, as well as tolbutamide, promazine and chlorpromazine.[5]

All three turbidity tests reveal pseudoalbuminuria in the presence of the aforementioned nonprotein metabolites. It should be noted that this effect is transitory, with a duration of 1 day to not more than 3 days.

When pseudoalbuminuria is suspected to be a laboratory artifact, currently available reagent tablets, or impregnated strips such as albutest and albustix, which do not depend upon turbidity readings but rather are based on a colorimetric index, should be employed. Needless to say, pseudoal-

buminuria following the ingestion of cholecystographic media does not connote any form of renal insufficiency.

A clear understanding of the properties of a cholecystographic medium and its fate and elimination will enable the radiologist to arrive at a better clinical diagnosis when confronted with the clinical complexities and imponderables of poor or nonvisualization. It is essential that he be familiar with the patient's history and clinical data when contemplating cholecystography so that he can exclude faulty intestinal absorption, hepatic derangement, acute abdominal disease such as peritonitis and pancreatitis, or disorders of intestinal motility such as hyperthyroidism, as possible causes for poor or nonvisualization.

The high absorption index and the predominantly hepatic-biliary elimination of a cholecystographic contrast agent grant the reliability that is needed for a more specified roentgenologic diagnosis; hence, this narrows the margin of diagnostic errors.

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Representatives on the National Committee on Radiation Protection: Robert Robbins, Philadelphia, Pa.; Herbert M. Parker, Richland, Wash.

Representative on the Board of Chancellors of the American College of Radiology: Milford D. Schulz, Boston, Mass.

Forty-fifth Annual Meeting: Mark Hopkins Hotel, San Francisco, Calif., April 1–4, 1963.

EDITORIALS

FLEXIBLE ROUTINE IN GASTROINTESTINAL EXAMINATION

TO THE BUSY roentgenologist facing each day a seemingly larger volume of gastrointestinal examinations, a methodical routine of procedure is exceedingly helpful. The examiner must remember, however, that a standard routine is not applicable to all patients. Flexibility of the examiner's mind as well as his response to different requirements for individual examinations is demanded if the highest quality of service is to be offered each patient. Skilled technical assistants, if they know the problem presented in a particular instance, are able to apply this same flexibility to the roentgenographic examination after fluoroscopy. Thereby, they may best demonstrate the desired anatomic or pathologic detail.

There are great virtues in a routine method of examination. The patient proceeds in orderly fashion from one phase of the examination to the next. All of the physician's assistants know what happens next and what is expected of them. Useless motion, clumsy procedure, loss of time, errors of omission, and confusion of personnel may be largely eliminated. When each person knows what to do, orderly progress in each examination and in a series of examinations is achieved. After persons work together for some time on a standardized routine, smoothly functioning teamwork develops and permits completion of many more examinations with less friction and wasted effort. This integrated and understanding cooperation can produce systematized examinations, comparable to the finesse exhibited by a surgical team in the operating room. Such is the virtue of a completely conceived and fully realized routine. Customary procedure in roentgenography has additional virtues. The roentgenograms are comparable to standard normal studies and are reproducible in subsequent examinations. These are diagnostic advantages in determining slight variations from normal and in judging the progress of disease.

Two other less obvious virtues of routine are that more persons can be examined by the individual roentgenologist and that the individual patient may receive less exposure to ionizing radiation in a relatively short, standardized type of examination. There are philosophical overtones in these virtues. In which type of examination has the roentgenologist achieved the greater benefit for mankind: the long examination done on fewer patients or the shorter examination of numerous patients? In which examination has the roentgenologist best performed for humanity—the tedious, more complete examination with greater radiation exposure of the patient, or the briefer examination with less risk and somewhat less accuracy? Although imponderable issues, these are factors meriting consideration when the work of different radiologists is evaluated.

The greatest disadvantage in standardization of roentgenologic examination—and the factor that demands constant realization of the possible need for flexibility—is that the anatomic relations of normal patients are variable and the manifestations of asymptomatic anomalous development may be even more divergent from the average. Pathologic processes produce a still broader variety of changes.

In a practice in which the roentgenologist is examining a limited number of patients, it is conceivable that each patient may receive a roentgenoscopic examination which

is complete in every detail. As the number of patients per roentgenologist increases, the time and effort that can be devoted to each decreases. For a given roentgenologist, the number of roentgenoscopic examinations that can be performed depends on the equipment and assistants available, the type of patients coming for examination (ambulatory, wheelchair, stretcher), the physical stamina of the examining physician, and the extensiveness of the individual examinations. The maximal work load that one can attain in any one day or week usually cannot be repeated on a continuing schedule.

Personal experience leads to the conclusion that a fairly strict basic routine of roentgenoscopy permits the roentgenologist to participate in fluoroscopy of the greatest number of examinations on a continuing basis. The incidence of error can be kept reasonably low provided the examiner performs his routine procedure with conscientious attentive concentration, aware at each step that variations in the examination may be required if the routine method does not result in satisfactory demonstration of the area or organ being studied.

A list of possible variations in technical maneuvers during roentgenologic examination would require several pages. Some of the more frequently useful variations might include a Trendelenburg study for esophageal varices, use of an opaque pill to verify a possible stenotic lesion, dilatation of the gastric fundus with gas to visualize its outline, barium-air contrast study of the antrum of the stomach to demonstrate mucosal detail, erect Bucky roentgenograms of the transverse type of stomach to show better the contour of the lesser curvature, left anterior oblique projection of the duodenal bulb for posterior ulceration, supplementary oblique or anteroposterior projections of the small intestine to compensate for overlapping loops, oblique or decubitus roentgenograms of the colon if the usual ones are indecisive, postevacuation roentgenogram after an air-contrast series if a polyp is suspected, roentgenoscopic study of the terminal ileum in the postevacuation phase of colonic examination, and immediate re-examination of the colon if the findings in the initial roentgenoscopic and roentgenographic examinations remain equivocal.

As new methods of examination and fresh concepts of procedure are reported, the roentgenologist may try them to determine their usefulness in his work. In this fashion he may keep his own procedure up to date and expand the variations in examination available to him to fit individual circumstances.

A basic routine of procedure, concentrated attention during the examination, and flexible variation of procedure when the standard routine is individually inadequate are the foundations for the successful performance of a large number of roentgenoscopic examinations with a minimum of diagnostic error.

Seymour Fiske Ochsner, M.D.

3503 Prytania Street
New Orleans, Louisiana

REGISTRY OF RADIATION PATHOLOGY

TO FURTHER the understanding of the nature and genesis of radiation effects in man and animals, a *Registry of Radiation Pathology* has been established within the American Registry of Pathology. It becomes the 26th registry in the system and, like the others, operates under the auspices of the National Research Council of the National Academy of Sciences and is located at the Armed Forces Institute of Pathology in Washington, D. C. This new registry is sponsored by the Division of

Radiological Health of the U. S. Public Health Service, Department of Health, Education, and Welfare.

Its physical location at the Institute and its membership in the American Registry make available to the Registry of Radiation Pathology unparalleled resources for the study of radiation effects in a uniquely suitable environment. Close cooperation among the several registries is inherent in the system.

The mission of the Registry of Radiation Pathology will be to collect, in useful numbers, materials having present or potential value; to classify these materials making them readily available for study; to collate, investigate, and analyze what is known about radiation-induced lesions; to perform follow-up studies whenever possible; to do research; and to make resources of the Registry available for educational purposes.

The Registry will provide a variety of opportunities for training to qualified persons from both the armed services and civilian life. Future plans include residency and fellowship training in radiopathology. Qualified scientists may also come to the Armed Forces Institute of Pathology (AFIP) for shorter periods of individual study. Training aids and study sets of microscope and lantern slides will be prepared for loan.

Through the AFIP, consultation service may be obtained by contributing pathologists. In this manner, the extensive files of the Institute can serve as a source of reference for comparison. The Registry, in turn, may seek consultation from the staff of the Institute and from authorities throughout the world.

The Registry of Radiation Pathology will be interested in cases of clinical, experimental, accidental, occupational, and natural exposure. Hopefully, it will attract pathologic material not only from this country but from throughout the world.

The prime requisite for inclusion into the Registry is a history of irradiation attested by detailed clinicopathologic information and precise radiation data for each entry. Upon being accessioned, contributions to the Registry will be classified on IBM cards. In this way the material will be readily accessible to a widely divergent group of interests.

Material that is desired includes both surgical and autopsy specimens accompanied when possible by slides, photographs, roentgenograms, clinical histories, and investigational data. All material received will be reviewed by the staff of the Registry and, if accepted, will be accessioned into the Registry. To facilitate the initial acquisition of specimens, the Registry urges all who feel they have a valid contribution to submit first a brief informational abstract concerning the material. Forms outlining the specific information desired will be made available on request.

Albert W. Hilberg, M.D.

Armed Forces Institute of Pathology
Washington 25, D. C.



VINCENT CLIFTON JOHNSON
1902-1962

THE SUDDEN, unexpected death of Vincent Clifton Johnson on June 10, 1962, has deprived medicine in Detroit of a respected physician, his associates of a needed and valued partner, and his family of an ideal husband and father.

Vin, as he was affectionately known, was born in Mt. Horeb, Wisconsin, on January 22, 1902. He graduated from the University of Wisconsin Medical School in 1927 where he was admitted to the Alpha Omega Alpha honorary fraternity. A two year internship in St. Mary's Hospital in Madison, Wisconsin, was followed by a two year residency in

radiology in the University Hospital at the University of Pennsylvania under Dr. Henry Pancoast. In 1931 he became an instructor in the Department of Roentgenology in the Medical School of the University of Michigan, and was Associate Professor when he left in 1942, to go to Detroit, Michigan, to join Dr. Lawrence Reynolds and his group, where he remained until the time of his death. He also held the position of Associate Professor of Roentgenology in the Wayne State University College of Medicine in Detroit.

Dr. Johnson was a member of the American Medical Association, the American Roentgen Ray Society, the Radiological Society of North America, and a Fellow of the American College of Radiology. He served the latter organization under his friend, Sam Donaldson, in the placement bureau. He was a member of the Detroit Roentgen Ray and Radium Society, and had served as its President.

These significant but dry data are the less important part of Vin Johnson's life. They were necessary stepping stones in the broader stream of his principal interest—people. He loved all people, not with regard for their social status or economic importance, but simply because they were individuals, and their value to him depended not on their accomplishments but on their sincerity and honesty. His residents (including this humble admirer), his friends, and his acquaintances were all important to him, and many at one time or another sought and received sympathetic understanding and advice from him. His inherent attribute in these relationships was kindness; he was known to remain protectively silent even when silence might imply his culpability, rather than to say an unkind or unnecessarily hurtful thing. He had the uncommon and happy faculty of being able to meet the great and the small on equal levels, and both the hospital trustee and the hospital orderly called him friend. He was never lonesome, because he sought out people, and they sought him.

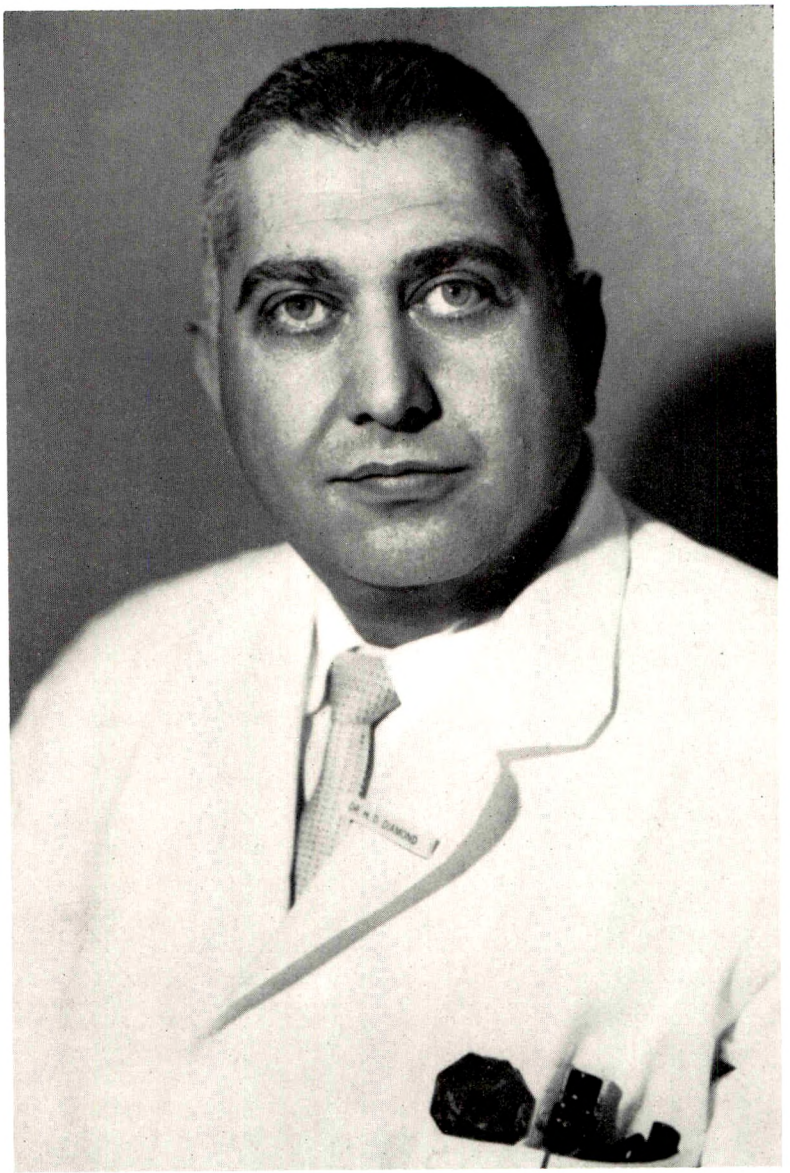
Vincent Johnson's special field was roentgenology of the head, and he had written well substantiated, carefully detailed articles, alone and in collaboration, on roentgenography of brain tumors, particularly on ventriculography of mid-brain tumors and on diseases of the temporal bone and the paranasal sinuses. His work in these fields was so well known that he was asked by the American Academy of Ophthalmology to give a refresher course at their national meeting. He was awarded a medal for an exhibit on brain tumors at the American Roentgen Ray Society meeting in 1934.

Like so many radiologists, he was a physician's physician. He was never happier professionally than when he was conducting a medical conference, or when he was consulting with fellow physicians. To him the patient had received less than enough if he and the neurosurgeon did not discuss the roentgenographic findings face to face, and this type of practice served only to increase his extensive and exact knowledge of neuroanatomy.

He treasured his private life; he, his wife Eleanor, his daughter Jaynor, and his son Vincent were a close and happy family. Vacations were always spent together, and his family participated in many of his hobbies. For years he had been active in amateur radio transmission and reception. He built his own equipment, including a television receiver, and was more than an amateur in tape recording. With an electronics engineer he formed a recording company, recorded organ music on stereotapes, and sold recordings commercially. Photography was another consuming interest.

Vin's death profoundly affected his family and friends by its suddenness. His life was full, and because he gave more than he received, he left the world a better place than he had found it.

E. F. Lang, M.D.



HENRY DAVID DIAMOND
1918-1962

HENRY DAVID DIAMOND died April 18, 1962, in Memorial Hospital. He was a victim of Hodgkin's disease, to the study and treatment of which he had devoted much of his professional life.

Born December 25, 1918, he attended the public schools of his native New York City, going then to the University of Louisville, where he received his Bachelor of Arts degree and where he graduated in medicine in 1944. Then, in 1945, while he was serving as lieutenant, junior grade, in the United States Naval Reserve, the disease from which he died 17 years later first made

itself known. After treatment at the Naval Hospital, Brooklyn, he was referred, in anticipation of medical discharge from the service, to Memorial Hospital in early 1946 for further care. There his intelligence and interest became obvious and he was given, after a short period as an observer, an appointment as an assistant in medicine, and then as a resident. In 1948 he became a junior member of the attending staff as clinical assistant. From then on his advancement, in recognition of his worth, was rapid, and on July 1, 1959, he succeeded to the position of chief of the Lymphoma Service. This promotion was heartily advocated by the retiring chief, his physician. Along with his advancement in the hospital staff at Memorial and James Ewing Hospital went corresponding advancement in his academic rank at Cornell University Medical College. In 1958 he became an associate professor of clinical medicine. His ability in clinical research was recognized by appointments and promotions in the Sloan-Kettering Institute, and on July 1, 1957, he became an associate and section head.

Dr. Diamond was an active member of some 20 medical and scientific societies, including the International Society of Hematology, the Harvey Society, the American Association for Cancer Research, and the American Radium Society, and he was a fellow of the American College of Physicians.

As chief of the Lymphoma Service Dr. Diamond had far-seeing plans for the future of the service. Beginning in 1956 he had been entrusted by his chief with executive responsibility for the recruitment, training and research activities of the special fellows of the service. Under his stimulation and guidance, the special fellows prepared between 1956, when the first one was appointed, and 1962, 15 important publications, representing their study of various features of lymphomas and leukemias. Moreover, during that time alone, 7 other papers bore Dr. Diamond's name as co-author, and his monograph *The Medical Management of Cancer*, published in 1958, received wide acclaim. His chief's foreword for the monograph includes the following: "The author of this monograph concerning certain major types of cancer amenable to treatment by the internist stepped into this field only a little over a decade ago, by joining what has become the Medical Neoplasia Service of the Memorial Center for Cancer and Allied Diseases. In this relatively short time he has not only witnessed, but indeed has actively participated in, the exciting progress in cancer that has taken place during these years. At the same time he has made himself thoroughly familiar with advances in the older technics of investigation and treatment of the cancer patient as a whole. Partially attesting to his broad experience with, and knowledge of, cancer as an internist are the numerous items bearing his name in the bibliography —items which could not have been omitted or reduced without seriously impairing the value of these references."

The sudden tragic death of his wife Rhoda in early January, 1960 during their return from a brief vacation dealt Dr. Diamond a blow from which his spirit never recovered. This unfortunate happening may well have contributed to his final unresponsive physical relapse, evident about 7 months before his death. Despite much discomfort he continued to see his patients until 2 weeks before his death. Thus ended the promising career of another physician dedicated to combatting in others the disease from which he himself suffered.

Lloyd F. Craver, M.D.

NEWS ITEMS

RADIOLOGÍA INTERAMERICANA

The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine welcomes with pleasure the publication of the new journal, *Radiología Interamericana*, which made its first appearance in June, 1962. This new journal is the official organ of the Interamerican College of Radiology and will be issued as a quarterly Journal of Radiology and Nuclear Medicine. Its distinguished Editor is Dr. Juan A. del Regato, Penrose Cancer Hospital, 2215 North Cascade Avenue, Colorado Springs, Colorado, U.S.A., and the members of the Editorial Committee are: Dr. Fernando Bloedorn, Chairman, Baltimore; Dr. Walter Bomfim-Pontes, São Paulo; Dr. Manuel Concha, Santiago de Chile; and Dr. Manuel Malenchini, Buenos Aires.

Only original articles in the Spanish and Portuguese languages will be published. The printer is R. R. Donnelley and Sons, Chicago, Illinois, U.S.A.

The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine extends its good wishes for success and distinctive progress.

MIDWINTER RADIOLOGICAL CONFERENCE

The Fifteenth Annual Midwinter Radiological Conference, sponsored by the Los Angeles Radiological Society, will be held at the Biltmore Hotel, Los Angeles, California, on Saturday and Sunday, February 2nd and 3rd, 1963.

An outstanding program of pertinent interest has been arranged and the guest speakers will be Doctor Ingmar Wickbom, Göteborg, Sweden; Doctor Robert E. Steiner, Hammersmith Hospital, London, England; Doctor Walter T. Murphy, Roswell Park Memorial Institute, Buffalo, New York; and Doctor John A. Campbell, Indiana University Medical Center, Indianapolis, Indiana.

The conference fee of $25.00 includes two luncheon meetings featuring questions and answers. A banquet ($7.50 per plate), preceded by cocktails, will be held Saturday evening at the Biltmore Bowl. Reservations may be made through A. W. Reiter, M.D., Secretary-Treasurer, 2632 East Washington Street, Pasadena, California.

Courtesy cards will be available to residents in Radiology and Radiologists in the Armed Forces by advance registration, with reduced tariff for luncheons and banquet.

Hotel reservations should be made promptly through the Convention Manager, Biltmore Hotel, Los Angeles, California.

EASTERN CONFERENCE OF RADIOLOGY

The Eastern Conference of Radiology will be held in Philadelphia, Pa., at the Bellevue-Stratford Hotel on April 4, 5 and 6, 1963. The program will include refresher courses sponsored by the Radiological Society of North America. There will also be papers on the program presented by pararadiological colleagues to be discussed by radiologists. A special lectureship will be sponsored on Friday, April 5, 1963.

For further information, please contact Luther W. Brady, M.D., Secretary, Eastern Conference of Radiology, 230 North Broad Street, Philadelphia, Pennsylvania.

THE AMERICAN SOCIETY OF X-RAY TECHNICIANS

The American Society of X-Ray Technicians is holding its Thirty-fifth Annual Convention at the Penn Sheraton Hotel in Pittsburgh, Pennsylvania, May 25–30, 1963.

Those interested please write to Frank R. Capezio, R.T., Chairman of Publicity, United States Steel Corporation, 1 Library Place, Duquesne, Pa.

FIRST INTERNATIONAL CONGRESS FOR STEREOLOGY

The First International Congress for Stereology will take place in Vienna from April 18th to 20th, 1963.

Stereology, which is the science of the three-dimensional interpretation of flat images, embraces many scientific disciplines. Problems of spatial interpretation arise in all branches of microscopy (including the use of the electronic microscope) and in astronomy as well. Important uses of stereology include the microscopical examination of medico-biological and anorganic structures (crystallography, metallography, mineralogy); an attempt is made to obtain exact knowledge of structural shapes by applying relevant mathematical theories and graphic reconstruction.

The Congress will deal with topics pertaining to these aspects.

Those wishing to attend please write to Dr. H. Haug, Secretary General, Wiener Medizinische Akademie, Aserstrasse 4, Vienna IX, Austria.

FELLOWSHIPS FOR TRAINING IN THERAPEUTIC RADIOLOGY

Under a Training Grant of The National Institutes of Health, the Penrose Cancer Hospital of Colorado Springs will expand its capacity for training of therapeutic radiologists. Residents in training will be assigned fellowship stipends of from $400.00 to $600.00 a month during the course of training in radiotherapy. The plan of training is divided in four years; appointments are made for one year and renewed.

This course of training prepares the resident for Certification in Therapeutic Radiology by the American Board of Radiology.

Candidates for initiation in this plan of training will be considered for positions open July 1st, 1963; appointments will be made at the end of 1962.

Address inquiries to: J. A. del Regato, M.D., Director, Penrose Cancer Hospital, Colorado Springs, Colorado.

COURSE IN MAMMOGRAPHY

A course in Mammography will be held in Philadelphia on November 2nd and 3rd, 1962 by the members of the Department of Radiology, Albert Einstein Medical Center, Northern Division. The program will consist of lectures on Technique, Anatomy, Physiology and Pathology of the breast with correlation of the roentgen findings.

The fee will be $35.00 to include lunch.

Please write to Simon M. Berger, M.D., Chief, Diagnostic Radiology.

THE WORLD MEDICAL ASSOCIATION

The United States Committee of The World Medical Association is engaged in a Doctor-to-Doctor Program to supply current medical journals to colleagues overseas. At first directed to Asia, it has now spread to Africa and Latin America. There are more requests for journals than can be supplied. Your valuable help is earnestly solicited.

Please send your name, address and titles of journals you will contribute to Ada Chree Reid, M.D., Chairman Doctor-to-Doctor Program of the United States Committee, The World Medical Association, 10 Columbus Circle, New York 19, N. Y.

BOOK REVIEW

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Radiation Therapy in the Management of Cancers of the Oral Cavity and Oropharynx. By Gilbert H. Fletcher, M.D., Radiotherapist; and William S. MacComb, M.D., Surgeon, Chief of Head and Neck Service; with the collaboration of Alando J. Ballantyne, M.D., Associate Surgeon, Head and Neck Service; Physics Section, The Calculation of Dose Interstitial Implantations by Robert J. Shalek, Ph.D., Associate Physicist and Marilyn Stovall, B.A., Senior Dosimetrist, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Cloth. Price, $16.50. Pp. 396, with numerous illustrations. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1962.

This new monograph on the radiation management of malignant tumors of the oral cavity and oral pharynx fulfills a much needed place in the radiation therapist's library. Most previous texts oriented to this group of diseases have presented standard techniques for lesions of given clinical extent and anatomic location. Written by two undisputed authorities in their respective fields—Dr. Fletcher (radiation therapy) and Dr. MacComb (head and neck surgery), supplemented by the valuable contributions of Drs. Ballantyne and Shalek and Miss Stovall—surgical indications rather than technique are expounded and the close integration of extensive irradiative and surgical procedures is described. The success of this combined approach depends, in part, upon the surgeon's acceptance of, and his ability to deal with, iatrogenic irradiative complications.

Since the cancers of these anatomic sites comprise less than 5 per cent of all human cancers, it is difficult for a single physician to gain an extensive experience in treating these lesions. Some are best controlled by irradiation, others by surgery, and still others by a combined application of the two methods. In this integrated approach, clinical varieties, indications for irradiative and surgical treatment, patient care, and the management of complications are stressed.

Developed from an instructional manual in use for 10 years and then formulated into a teaching text and further evaluated for a 4 year period, this volume is succinctly organized. Those lesions arising in the anterior two-thirds of the tongue, floor of the mouth, buccal mucosa, upper and lower gums, faucial pillars, soft palate, tonsillar bed, glossopalatine sulcus, base of the tongue and pharyngeal walls are thoroughly described. The causes of treatment failure and the treatment of complications are discussed.

In an excellent physics section designed to be a comprehensive manual for the calculation of dosage delivered by interstitial implantations based on the Manchester system, the determination of dosage from perpendicular radiographs and three-dimensional reconstructions is discussed. Deviations from the Paterson and Parker rules, the use of "Indian club" and "dumbbell" needles, radioactive materials used as radium substitutes, the use of radioactive seeds for volume implants and an explanation of dose distribution around radium needles and implants are also described in detail.

Four appendices give basic definitions and concepts relative to radioactivity, the description of the Sievert integral Paterson and Parker tables and graphs, and formulae for areas and volumes.

An adequate number of illustrations portray isodose distributions and the location, configuration, and volume of interstitial implants. Photographs and diagrams of the location and clinical extent of various lesions further illustrate the text.

This book, published as a monograph in the American Lecture Series in Radiation Therapy, under the editorship of Dr. Milton Friedman, is another outstanding contribution from the authors' institution and will be an invaluable aid to those charged with the responsibility of treating this rather difficult group of malignancies.

K. L. Krabbenhoft, M.D.

BOOKS RECEIVED

GYNECOLOGY. By Langdon Parsons, M.D., Professor of Obstetrics and Gynecology, Boston University School of Medicine; Chief of Gynecology, Massachusetts Memorial Hospitals; and Sheldon C. Sommers, M.D., Pathologist, Scripps Memorial Hospital. Cloth. Price, $20.00 Pp. 1,250, with numerous illustrations, many in color. W. B. Saunders Company, 218 W. Washington Square, Philadelphia 5, Pa., 1962.

PATHOLOGY OF THE LUNG. By H. Spencer, M.D., Reader in Morbid Anatomy & Histology in the University of London; Honorary Consultant Pathologist to St. Thomas's Hospital, London, England. Cloth. Price, $30.00. Pp. 850, with numerous illustrations. The Macmillan Company, 60 Fifth Avenue, New York 11, N. Y., 1962.

A TEXT-BOOK OF X-RAY DIAGNOSIS. Vol. II. Third edition. Edited by S. Cochrane Shanks, C.B.E., M.D., F.R.C.P., F.F.R., Consultant Radiologist, University College Hospital, London; and Peter Kerley, C.V.O., C.B.E., M.D., F.R.C.P., F.F.R., D.M.R.E., Director, X-Ray Department of the Westminster Hospital and the National Heart Hospital, London, England. Cloth. Price, $27.00. Pp. 991, with 819 illustrations. W. B. Saunders Company, 218 W. Washington Square, Philadelphia 5, Pa., 1962.

THE INTERPRETATION OF TOMOGRAMS OF THE HEAD; AN ATLAS. By Marvin L. Daves, M.D., Assistant Professor, Department of Radiology, University of Colorado Medical Center, Denver, Colorado; and William E. Loechel, Director of Medical Illustration, Henry Ford Hospital, Detroit, Michigan. Cloth. Price, $17.50. Pp. 248, with 172 illustrations. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1962.

MYELOGRAPHY. By Robert Shapiro, M.D., Chairman, Department of Radiology, The Hospital of St. Raphael, New Haven, Connecticut; Associate Clinical Professor of Radiology, Yale University School of Medicine. Cloth. Price, $11.00. Pp. 278, with 236 illustrations. Year Book Medical Publishers, 35 East Wacker Drive, Chicago 1, Ill., 1962.

RADIODERMATITIS. By Ervin Epstein, M.D., Associate Clinical Professor of Dermatology, University of California Medical School; Chief of Dermatology and Syphilology, Highland-Alameda County Hospital; Consultant to Oakland Area Veterans' Hospital; Formerly, Associate Clinical Professor of Medicine (Dermatology), Stanford University Medical School; Diplomate of American Board of Dermatology and Syphilology. Cloth. Price, $7.75. Pp. 178, with many illustrations. Charles C Thomas, Publisher. 301–327 East Lawrence Avenue, Springfield, Ill., 1962.

THE YEAR BOOK OF CANCER (1961–1962 Year Book Series). Compiled and edited by Randolph Lee Clark, M.D., Director and Surgeon-in-Chief, The University of Texas M. D. Anderson Hospital and Tumor Institute; Professor of Surgery, The University of Texas Postgraduate School of Medicine; Clinical Professor of Surgery, Baylor University, College of Medicine; Chairman, Committee on Cancer, American College of Surgeons; and Russell W. Cumley, B.A., M.A., Ph.D., Director of Publications; The University of Texas M. D. Anderson Hospital and Tumor Institute; Professor of Medical Journalism, The University of Texas Postgraduate School of Medicine; Executive Editor, Medical Arts Publishing Foundation, Houston, Texas. Cloth. Price, $8.50. Pp. 527, with 184 illustrations. Year Book Medical Publishers, 35 East Wacker Drive, Chicago 1, Ill., 1962.

RÖNTGENDIAGNOSTIK DER SÄUGLINGSPNEUMONIEN. By Dr. K. Gefferth, I. Universitäts-Kinderklinik, Budapest, Hungary. Cloth. Pp. 232, with 281 illustrations. Kultura, P. O. Box 149, Budapest 62, Hungary, 1962.

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ROENTGEN DIAGNOSIS

Head

Ambrosetto, Cesare. Post-traumatic subdural hematoma: further observations on nonsurgical treatment. *A.M.A. Arch. Neurol.*, Apr., 1962, *6*, 287–292. (From: Clinica delle Malattie del Sistema Nervoso dell'Università di Bologna, Bologna, Italy.)

The author reports 3 cases considered to have chronic subdural hematomas in which the clinical symptoms and the characteristic arteriographic picture regressed completely without surgical intervention. The treatment consisted of bed rest and an ample diet fortified with a variety of vitamins, antihemorrhagic and vasoprotective drugs, corticosteroids and intravenous injections of hypertonic glucose solutions.

All of these patients were in the age group between 50 and 60 years and the time interval between head injuries and the appearance of neurologic difficulties was from 2 to 3 months. The clinical improvement was accompanied by normalization of the previously altered electroencephalographic and angiographic picture and disappearance of the lesion.

These 3 patients, as well as 4 reported elsewhere were considered symptom-free and repeated follow up studies did not show signs of recurrence in any of them. Other such patients are still under observation and are not included as they warrant a longer follow-up.—*Arthur E. Childe, M.D.*

Brusori, G., and Garusi, G. F. Indicazioni e possibilità diagnostiche della sialografia nelle affezioni delle ghiandole salivari. (Indications and diagnostic possibility of sialography in lesions of the salivary glands.) *Radiol. med.*, Jan., 1962, *48*, 12–30. (From: Istituto di Radiologia e del Radio dell'Università di Bologna, and Ospedale Civile S. Croce, Cuneo, Italy.)

All authors agree that there are no substantial contraindications to sialography. In cases of subacute infectious parotitis, the topical action of the iodinated medium may have a therapeutic effect. In some instances the contrast substance may be combined with antibiotics.

Sialography of the parotid and of the submaxillary glands has demonstrated the following:

1. Marked variability in the morphology and in the dimensions of the normal salivary glands.

2. Dependent on the pressure of the injection and on the quantity of the liquid used, two characteristic results are obtained. In one the opacification is limited to the excretory paths. In the other, there is also a visualization of the acini and of the parenchyma.

3. The investigation is indicated in the study of malformations and of congenital abnormalities (cysts, fistula, ectopia, anomalies of the principal excretory ducts). It is likewise of use in acquired affections (lithiasis, inflammatory processes, degenerative diseases, benign and malignant neoplasms, post-traumatic lesions).

4. The method may also be valid in the more exact determination of extrinsic pathologic processes.—*Anthony A. Blasi*, M.D.

Neck and Chest

Ettman, Irving K., and Keel, Daniel T., Jr. Tracheal diverticulosis. *Radiology*, Feb., 1962, *78*, 187–191. (From: The Department of Radiology, Veterans Administration Teaching Group Hospital, Memphis, Tenn.)

Tracheal diverticulosis may be suspected when the conventional chest roentgenogram shows widening of the trachea and major bronchi in both their anteroposterior and transverse diameters, and evidence of recurrent infection of the lung parenchyma as exhibited by interstitial fibrosis, emphysema, and recurrent pneumonitis. It is characterized by single or multiple outpouchings of the tracheal mucosa either between the tracheal cartilages or through the trachealis muscle posteriorly. It may be diagnosed on bronchographic examination by confirmation of tracheal and bronchial widening, and visualization of multiple shallow widemouthed outpouchings of the tracheal and major bronchial mucosa, predominantly posteriorly. The bronchogram also will show extensive bronchiectasis throughout the lung fields, with the bronchi revealing a peculiar beaded appearance.

Three case reports are presented, and comment is made that although the condition is considered rare, it is evidently not always demonstrated bronchographically. Protrusion posteriorly through the trachealis muscle is apparently easier than laterally through the fibroelastic tissue. The etiology is not established, although a congenital predisposition may be present. A large number of cases of chronic lung disease were reviewed, but the disease was not found; therefore, there must be some inherent weakness. Symptoms were associated with the chronic lung disease rather than with the diverticula themselves.—*James C. Moore, M.D.*

Elliott, G. B., Belkin, A., and Donald, W. A. J. Cystic bronchial papillomatosis. *Clin. Radiol.*, Jan., 1962, *13*, 62–67. (From: Department of Clinical Pathology, Calgary General Hospital, and Provincial Cancer Clinic, Calgary, Alberta, Canada.)

The pseudo-stratified ciliated epithelium of the respiratory tract shows a pronounced tendency to diffuse papillomatosis over long periods. This is seen characteristically in the nose and paranasal sinuses in adults where eventual malignancy is common and

in the laryngotracheal region in children where malignant transformation is very rare. Similar proliferations occur occasionally in bronchi in adult life producing coin lesions or cysts. The authors present a case report and a review of the condition which has escaped mention in standard reference texts.

A 52 year old Ukranian boiler scaler was first seen in September 1953 because of transient pleuritic pain in the left chest. Roentgenograms of the lungs showed an ill-defined opacity in the apex of the left lower lobe. The lesion remained unchanged over a one month period and no specific cause could be found for it or for the pleurisy. The patient was uncooperative and was not seen again until March 1955, when the roentgenogram revealed extension of the lesion and central cavitation, but further investigation was refused. The patient reappeared in September 1956 because of paroxysmal dry cough and a small hemoptysis. Clubbing of the fingers and toes which had been questionable at the first examination was now quite evident. The general condition was good. Chest roentgenograms revealed a 3 cm. thin-walled cavity with fluid level in the apical segment of the left lower lobe. The sputum contained some blood but no tumor cells and the culture produced a species of *Candida*. The bronchoscopy was negative. The patient left the hospital against advice.

In October 1957, he returned because of a massive hemoptysis. Roentgenograms showed a considerable enlargement of the lesion and persistent cavitation. Repeated sputum cultures for tubercle bacilli and carcinoma cells were negative. After blood transfusion, the patient felt well and again left against advice.

In September 1958, he finally consented to full investigation. The lesion in the left lower lobe had further enlarged and again showed a fluid level. The bronchoscopy revealed a firm papillary tumor protruding through a widened apical left lower segmental bronchus which on biopsy proved to be squamous papilloma. Left pneumonectomy was performed; no mediastinal lymphadenopathy was seen. The specimen showed the main bronchus to the lower lobe to be ringed by firm grey papillary tissue reaching 3 mm. in thickness. The bronchus continued thus for 1.5 cm. and abruptly opened into a rounded cystic cavity 9 cm. in diameter which showed coarse cauliflower-like corrugated papillomatous projections up to 2 cm. in thickness. Microscopically, the cyst showed well differentiated squamous papillomatosis without keratinisation. No papillomata were found in other bronchi or bronchioles. The hilar lymph nodes were free from tumor.

The patient has remained well and able to work for 2 years. The clubbing of the fingers and toes has disappeared. There is no roentgen evidence of recurrence at present.

Histologically, the papillomata of the respiratory tract are identical in the nose, larynx, trachea, and the bronchi. Their epithelium is mostly a stratified squamous type, occasionally with the surface layer of ciliated respiratory columnar type. All are characterized by a tendency to multiplicity and persistent recurrence with progressively longer intervals of latency. Previously reported cases of papillomata of the bronchus have occurred in association with papillomata of the larynx and have usually been multicentric in the lungs. Malignant degeneration has been reported in one instance.

The cause of the condition is not known because human laryngeal papilloma has been produced in the similar vaginal mucosa of dogs by innoculation of cell-free filtrates.

The lesion can easily be confused with slow-growing cavitating epidermoid carcinoma of the bronchus. Umbilication is not seen in papillomatosis and the hilar lymph nodes are not involved. Histologically, also, the lesion has been confused with squamous cell carcinoma. The differentiation is particularly important since conservative surgery is adequate for papilloma and no more normal lung tissue than is absolutely necessary should be removed because of the possibility that other asymptomatic foci may later require further resection.—*Leslie K. Sycamore, M.D.*

Rodman, M. H., and Jones, C. W. Catamenial hemoptysis due to bronchial endometriosis. *New England J. Med.*, Apr., 1962, *266*, 805–808. (From: The Mount Auburn Hospital, Cambridge, Mass.)

The authors report the first patient proven to have had bronchial endometriosis. The patient, 26 years of age, complained of multiple single episodes of hemoptysis and blood streaked sputum. These episodes occurred with the onset of each menstrual period. Repeated roentgenographic examinations during the time of bleeding revealed a small area of increased density in the left first anterior interspace that disappeared in the interval between bleeding.

Surgical exploration and removal of this area was done. A nodule of ectopic endometrial tissue was found in the bronchial wall with a thick-walled small artery lying immediately adjacent to the nodule. This artery gave rise to an arteriole that penetrated deep into the nodule towards the surface and this probably was the source of the hemorrhages.

This is a most unusual and interesting cause of pulmonary hemorrhage.—*Frank J. Rigos, M.D.*

Slutzker, Berkeley, and Perryman, Peter H. Pulmonary alveolar proteinosis: response to nebulized enzyme therapy. *A.M.A. Arch. Int. Med.*, Apr., 1962, *109*, 406–413. (From: Veterans Administration Center, 4100 W. Third Street, Dayton, Ohio.)

The authors report a case of pulmonary alveolar proteinosis previously proven by lung biopsy which was successfully treated with streptokinase-strepto-

dornase enzyme aerosol. This 32 year old man had a history, symptomatology and other findings not strikingly different from other cases previously reported. Two courses of therapy were administered approximately one month apart. There was a marked subjective and objective improvement within a 10 day period. The patient remained objectively improved 6 months after the initiation of therapy and 5 years after the presumed onset of the disease.

The roentgenograms were considered grossly normal one month after the last treatment and they continued so for a 6 month period over which he was followed.

It is concluded that steroids seem contraindicated in the treatment of this disease but that iodides may be of some long-term value. Antibiotics seem indicated only during the acute course of a demonstrable infection.—*Arthur E. Childe, M.D.*

Kaftori, Joseph K., Bassan, Harry, Bellei, Baruch, and Griffel, Benjamin. Pneumocystis Carinii pneumonia in the adult: report of a primary case. *A.M.A. Arch. Int. Med.*, Apr., 1962, *109*, 438–446. (Address: Joseph K. Kaftori, M.D., Department of Internal Medicine, Rambam Government Hospital, Haifa, Israel.)

The authors present a well studied case of a 23 year old woman who died of pneumocystis Carinii pneumonia. In their opinion this may be the first published case of this condition occurring as a primary in the adult. That it commonly occurs as a primary in debilitated infants and prematures, usually with fatal outcome, is not disputed, but in adults pneumocystis Carinii is a secondary process observed in patients suffering from malignancy of the lymphoreticular system or from leukemia.

The literature relating to pneumocystis Carinii pneumonia is reviewed and the association of cytomegalic inclusion disease is pointed out.

The symptoms of progressive tachypnea, dyspnea, cyanosis and tachycardia, and the lack of objective chest findings, except for the roentgenographic changes, seen in children were present in the reported case. These are different from the manifestations in malignancy where evidence of the protozoan organism is found only at autopsy.

The association of pneumocystis Carinii pneumonia and hypogammaglobulinemia is noted and was present in the reported case.

The authors state that a definite diagnosis can be made only on a pathologic examination and during life only by lung biopsy. Other conditions which must be considered in the differential diagnosis are: Hamman Rich syndrome, pulmonary alveolar proteinosis, cytomegalic inclusion body pneumonitis, sarcoidosis, periarteritis nodosa, and military tuberculosis.—*George A. Kling, M.D.*

Croizat, P., Galy, P., Papillon, J., Revol, L., Chassard, J. L., Contamin, A., and Bretagnolle, G. Les formes médiastinales de début de la maladie de Hodgkin: à propos de 41 observations (Early mediastinal forms of Hodgkin's disease; report of 41 observations.) *J. de radiol., d'électrol. et de méd. nucléaire*, Jan.–Feb., 1962, *43*, 1–11. (From: Centre Pr. Léon-Bérard and Clinique médicale du Pr. P. Croizat, Lyon, France.)

It is widely accepted that in a number of cases of malignant lymphogranulomatosis the condition manifests itself as a localized rather than generalized disease. Furthermore, the behavior of the original or localized lesion makes it possible to forecast the expected behavior of the disease in general.

Precise evaluation of the incidence of mediastinal involvement in Hodgkin's disease is difficult. Statistics tend to be slanted and influenced by the experience and interest of the reporting investigator—surgeon, internist, or radiologist. The authors report 31 cases, or 11.3 per cent, of true mediastinal involvement in a series of 363 cases of Hodgkin's disease observed during a 25 year period. This is a higher incidence than that reported in the literature which varies between 2.6 and 8.9 per cent.

A review of a total of 2,657 cases collected from the French and foreign literature between the periods of 1935 and 1957 reveals a total of 89 cases, or 3.35 per cent, of Hodgkin's disease of the mediastinum. The age range extended from 9 to 52 years, with most of the patients under the age of 30.

In the authors' series the disease was discovered on a routine check up or during an examination of the patient because of definite systemic manifestations, consisting of general weakness, asthenia, anorexia, loss of weight, or low grade temperature suggesting typhoid fever. In 30 cases of Hodgkin's disease the following diagnoses were erroneously made, and treatment administered accordingly: typhoid fever, hyperthyroid disease, pneumonia, *Staphylococcus* septicemia, sarcoidosis, and mediastinal neoplasms. In 4 cases the roentgenologic appearance of the heart and mediastinum resulted in a diagnosis of cardiovascular disease. Several of the cases were treated for tuberculosis.

Involvement of the mediastinum in Hodgkin's disease, as observed reoentgenologically, may be limited to the anterior superior mediastinum, presenting a more or less "chimney stack" appearance, or may be localized to the hilar region, erroneously diagnosed as tuberculosis or saccoidosis. The changes may be unilateral or bilateral. The involvement may extend beyond the hilus into the lung simulating a pulmonary neoplasm. Finally, the disease may produce distortion of the contour of the heart and great vessels, presenting a configuration consistent with rheumatic heart disease or pericarditis.

Hodgkin's disease of the mediastinum does not remain intrathoracic for any considerable length of time, but tends to metastasize to the lymph nodes of the subclavian, carotid, and axillary regions. The involvement may be limited to a single area or to multiple areas. The interval between the development of the primary mediastinal lesion and the extrathoracic manifestation gives an indication of the over-all virulence of the disease, the course it will take, and the eventual survival of the patient.

The prognosis remains grave and the expected survival at the end of the first year is 83 per cent, at the end of the second year 50 per cent, at the end of the third year 33 per cent and at the end of the fourth year 25 per cent.

Once a definite diagnosis has been established, extensive therapy should be given, extended well beyond the apparent disappearance of the tumor or return to normal of the mediastinal shadow.—*William H. Shehadi, M.D.*

Heitzman, Edward J., Heitzman, George C., and Elliott, Charles F. Primary esophageal amyloidosis: report of a case with bleeding, perforation, and survival following resection. *A.M.A. Arch. Int. Med.*, May, 1962, *109*, 595–602. (Address: Dr. Edward J. Heitzman, Assistant Attending Surgeon, Department of Thoracic Surgery, St. Joseph's Hospital, Syracuse, N. Y.)

The authors report a case of primary amyloidosis with bleeding, perforation, and survival following resection, of the distal esophagus which at the time of surgery was considered to be carcinoma with perforation.

The authors give the following classification of amyloidosis:

I. *Primary amyloidosis*
   A. Systemic
   B. Tumefactive
   C. (The authors add a new primary) The familial amyloidosis

II. *Amyloidosis complicating myeloma*
   A. Systemic
   B. Tumefactive

III. *Secondary amyloidosis*
   A. Systemic
   B. Tumefactive

In 1935, Reimann, Kouchky, and Eklund presented the first case of primary amyloidosis diagnosed clinically. Since then, over 200 cases have been published.

Amyloid is an extracellular, homogeneous, hyaline material which first is deposited around the walls of the capillaries, then around the arteries, and finally on the surfaces of cells and connective tissue fibers. It may occasionally occur intracellularly.

The authors conclude that for the first time hematemesis and esophageal perforation are reported secondary to primary non-familial tumefactive amyloidosis of the esophagus.

This apparently is the first recorded successful resection of esophageal amyloidosis.

The authors also review the diagnostic features of primary amyloidosis.—*Peter C. Truog, M.D.*

Abdomen

Flood, Charles A., Wells, Josephine, and Harvey, Harold D. Prognosis in cancer of the stomach. *Am. J. Digest. Dis.*, May, 1962, *7*, 420–431. (Address: 180 Ft. Washington Avenue, New York 32, N. Y.)

The study is based upon a series of patients admitted to the hospital during an 8 year period from January, 1948 to January 1956 and all these patients were found to have carcinoma of the stomach. The series comprizes 426 patients with 390 having records sufficiently complete for the purpose of this study. Complete followup information was available in all but 10 cases. The 3-year survival rate for the group of 390 patients was 19 per cent and the 5-year survival rate was 11 per cent. The roentgenologic data were considered adequate for evaluation in all but 26 cases.

The entire series of patients was subdivided according to the location of the lesion as described roentgenologically. The stomach was arbitrarily considered to be divided into approximate thirds: the upper third was defined as the portion that is located at or above the level of the cardioesophageal junction, the middle third (pars media) as the area between the cardia and the incisura, and the lower third as the horizontal portion extending from the incisura to the pylorus. The largest proportion of the tumors was in the antrum and the smallest number in the upper third of the stomach. In the upper third 48 cases had definite roentgen diagnosis and 11 had indeterminate diagnosis; in the middle third 73 patients had a definite diagnosis while the diagnosis was indeterminate in 33; in the distal third 110 had a definite diagnosis and 36 had an indefinite diagnosis.

The roentgen findings were classified as being of indeterminate diagnostic significance even though the examining radiologist frequently favored a diagnosis of carcinoma. An essentially unequivocal roentgen diagnosis of neoplasm seemed justified in 77 per cent of all the patients. The final roentgen diagnosis made prior to operation was accepted although multiple opinions often were expressed after patients had undergone more than one roentgenologic examination.

The authors conclude that on the basis of the present data it appears that cancer of the stomach presenting a roentgen appearance which resembles that of a benign ulcer in the pars media has a better than average prognosis following surgical therapy.

The 5-year survival for a patient with cancer of the pars media who had roentgen findings but did not permit a definite diagnosis of neoplasm was 26 per cent as compared with the over-all 5-year survival of 11 per cent. Most of these patients presented a roentgen picture of an ulcer crater without clear cut evidence of a mass lesion. The 5-year survival of the group with cancer in the antrum was also approximately 25 per cent. The size of the ulcer appeared to play some part. A high incidence of tumors of 4 cm. or less in diameter was seen in this group; also, a high incidence of tumors which grossly resembled benign ulcer was observed.

The incidence of metastases to the lymph nodes was quite low in the carcinomas of the pars media and the antral area.

Diffuse antral narrowing may occur with carcinoma without diffuse neoplastic infiltration of the antrum. Some of the changes may be attributed to spasm of the muscular coat. Deformity of the distal antrum was also seen in a patient who had a carcinomatous ulcer located high in the stomach, without gross evidence of neoplasm in the region of the deformity in the antrum.

The relatively good prognosis of carcinoma of the stomach resembling benign peptic ulcer or benign antral disease should be considered in the evaluation of patients with such diagnostic problems. The opportunity to cure a favorable type of lesion may be lost if surgery is deferred for too long a time.—*Peter C. Truog, M.D.*

Harris, W. B., and Babbit, D. P. Early postoperative roentgenographic findings in congenital hypertrophic pyloric stenosis. *Surg., Gynec. & Obst.*, May, 1962, *114*, 630–633. (From: The Radiological and Surgical Departments of Milwaukee Children's Hospital, Milwaukee, Wis.)

Twenty-five consecutive infants who had congenital hypertrophic pyloric stenosis were examined preoperatively, then rechecked in a few days after surgery and again at ages from 24 to 39 months.

The authors' findings again confirm those of others that the persistence of a defect in the pyloric antrum should be expected postoperatively in patients with hypertrophic pyloric stenosis even though the pyloric opening time usually returns to normal immediately. In infants who have persistent symptoms, the opening time usually continues to be delayed. It is rarely necessary to reoperate on patients for pyloric stenosis.—*Frank J. Rigos, M.D.*

Oliva, L. Lo studio radiologico dei meccanismi di compenso del gastroresecato. (Radiologic study of the compensatory mechanism following gastrectomy.) *Radiol. med.*, Jan., 1962, *48*, 1–12. (From: Istituto di Radiologia dell'Università di Genova, Genova, Italy.)

A high percentage of patients with gastric resection following gastric or duodenal ulceration achieves a clinical cure. In view of the necessary surgical mutilation involved in the operation, this result attests to the great adaptability of the organism.

The normal stomach has three fundamental functions: (1) food storage; (2) digestive activity; and (3) regulation of the emission of the bolus into the intestinal tract.

The author discusses the postoperative compensatory mechanism in the Billroth I and the Billroth II types of resection. In the Billroth I type of resection, the stomach is reduced in size slightly. The second portion of the duodenum anastomosed with the gastric stump is dilated, endowed with motility, and simulates a new bulb in 79 per cent of the cases. In the Billroth II type of resection, the compensatory function of storage is at the expense of the efferent loop of the anastomosis. This loop is dilated and hypotonic.

The digestive capacity is poorly compensated. The peristalsis is weak in the gastric stump and, at first, lacking in the efferent loop.

It is interesting to note the compensatory mechanism in the control of the emission of the bolus into the intestine. It is initiated by short and superficial peristaltic waves in the pre-anastomotic portion of the resected stomach. The useful caliber of the anastomosis is that of the distal portion of the efferent loop. The flow of the contrast medium may be continuous through an incontinent stoma or may present a rhythmic, intermittent stream. This action is due solely to the tone and contractions of the efferent loop.—*Anthony A. Blasi, M.D.*

Burmeister, R. William. Intussusception in adult: elusive cause of recurrent abdominal pain. *Am. J. Digest. Dis.*, Apr., 1962, *7*, 360–374. (Address: 1515 Lafayette Street, St. Louis, Mo.)

Intestinal intussusception is rarely considered in the differential diagnosis of gastrointestinal disease in the adult, but the author has collected 32 such cases seen at the St. Louis University-affiliated hospitals over a 10 year period. The incidence per 1,000 adult medical and surgical admissions was approximately one-tenth of the incidence of intussusception on the pediatric service. Twenty-five cases were considered suitable for study.

Seventy-six per cent of the cases showed an associated probable causative lesion. Sixteen of these 19 had tumors equally distributed between malignant and benign. All except 1 patient gave a suggestive history of intermittent attacks of colicky pain, often increased by intake of food and frequently radiating to the right lower quadrant or the back or both. Fifty per cent of the patients showed a palpable mass which often changed rapidly or recurred. A positive guaiac test in the stool was the most useful laboratory

finding occurring in two-thirds of the patients.

On roentgen study, plain roentgenograms may show the characteristic homogeneous opacity and peripheral concentric ringing by translucent gas. Barium examination by meal in the enteric cases and by enema in the ileocecal and colonic cases reveals the characteristic picture sometimes also demonstrating a causal tumor. The examination should be done during an attack and the possibility of intussusception kept in mind by the examiner. The differential diaagnosis includes regional enteritis, ulcerative colitis, and partial obstruction due to band or foreign body. Correlation of clinical and roentgenographic findings should suffice for differentiation.

As distinguished from the situation in children in whom a barium enema may be curative, treatment in the adult calls for mandatory surgery because of the frequency of associated lesions. Prompt recognition and early treatment are particularly important in cases of intussusception complicating pregnancy which are associated with high maternal and infant mortality.—*Leslie K. Sycamore, M.D.*

Townes, Philip L., Wunderlich, Ray C., Jr., and Gerbasi, Michael J. Familial occurrence of malrotation of intestine. *J. Pediat.*, Apr., 1962, *60*, 555–560. (From: The Departments of Anatomy and Pediatrics, The University of Rochester School of Medicine and Dentistry, Rochester, N. Y.)

This report concerns a family in which 3 newborn siblings were found to have malrotation of the intestine with obstruction. It is believed that this is the first report of multiple occurrence of malrotation in a single sibship. All 3 were premature infants. The first was found to have a partial midgut volvulus and a cecum which was fixed in the left upper quadrant at laparotomy. At necropsy on the fourth day of life, the second sibling was noted to have a mobile cecum with gaseous distention of the small bowel, and multiple kinks of large bowel. The third sibling expired on the fourth day of life also. Postmortem examination revealed serosal adhesions and partial obstruction of the jejumun with incomplete rotation of the colon as well.

Although the precise pattern of heredity could not be determined, the authors suggest that the multiple occurrence of malrotation in this family may be due to hereditary factors. The available genetic data pertaining to this group of developmental anomalies are reviewed.—*Francis P. Shea, M.D.*

Zboralske, F. Frank, and Amberg, John R. Cholecysto-cholestasis: cause of cholecystographic error. *Am. J. Digest. Dis.*, Apr., 1962, *7*, 339–346. (From: Department of Diagnostic Radiology, Milwaukee County Hospital, Milwaukee 13, Wis.)

It has long been recognized that stasis of bile in the gallbladder in patients on a fat-free diet may be a reason for nonfilling in cholecystography. The authors were unable to find in the literature, however, any controlled series on normal persons and they, therefore, report a study of comparative examinations in 10 normal individuals. A first examination was done after 60 hours of a fat-free diet. At a second examination 3 months later, no dietary restrictions were prescribed until the evening before the roentgen study when a fat-free meal was taken prior to the ingestion of the contrast medium. In both series, 3 grams of iopanoic acid was the medium employed.

Six of the 10 subjects showed faint or absent visualization on the first test and normal visualization on the second. One showed no visualization on the first and faint visualization on the second. In 3 subjects, good visualization was obtained on both examinations.

The results indicate that a reliable roentgen study of the gallbladder necessitates a normal diet prior to examination. Cholecysto-cholestasis must be considered as an important source of error in patients who have had a fat-free diet, vomiting, or a limited food intake prior to examination particularly if the patient has been maintained on intravenous fluids.—*Leslie K. Sycamore, M.D.*

Siller, T., and Moore, S. Annular pancreas with duodenal enteroliths of biliary type: fifty years' survival following gastroenterostomy. *Canad. M.A.J.*, May, 1962, *86*, 830–833. (From: The Department of Pathology, Montreal General Hospital, Montreal, Quebec, Canada.)

An unusual complication of chronic duodenal obstruction is presented. The patient had a gastroenterostomy at 2 years of age for duodenal obstruction thought at that time to be secondary to tuberculous glands in the region of the pancreas. She did well for many years, but at the age of 42 developed gas, upper abdominal pains and diarrhea. An upper gastrointestinal series, at age 44, showed the gastroenterostomy functioning well. The afferent loop was dilated and ended in a grapefruit-sized blind pouch.

The symptoms progressed until 1961, when at age 52, she was admitted with fulminating enterocolitis and died due to staphylococcal septicemia.

Autopsy showed complete obstruction of the midduodenum with dilatation and muscle hypertrophy of the proximal portion. The obstruction was due to an annular pancreas, The proximal duodenum contained 3 liters of bile-stained fluid as well as numerous green calculi measuring 2 to 5 cm. in diameter. The gallbladder contained similar, but much smaller, calculi. The common duct was not dilated. A fistula was not demonstrated. Chemical analysis of the duodenal calculi showed them to be formed of bile and identical with gallstones.

The duodenal calculi may have originated primarily in the duodenum or from small stones passing

from the gallbladder, but the major portion of their bulk was formed in the duodenum. Bile stasis and the alkalinity of the duodenal contents were the contributing factors.—*Barry Gerald, M.D.*

Barrett, A. F. Gas in the portal vein: diagnostic value in intestinal gangrene. *Clin. Radiol.*, Apr., 1962, *13*, 92–95. (From: Radiodiagnostic Department, United Birmingham Hospitals, Birmingham, England.)

As a result of intestinal gangrene gas embolism of the portal vein may occur. The author gives 2 case reports of such: 1 following thrombosis of the lower one-third of the abdominal aorta and its main branches, with extensive gangrenous changes in the small bowel; and 1 with enterocolitis necroticans, with gangrenous changes from the duodenum to the anal canal. Both patients showed roentgenologic evidence of gas in the portal vein and its branches within the liver.

On a roentgenogram disclosing tapering linear and reticular translucencies in the right upper quadrant, in differential diagnosis one must consider gas within the portal venous system of the liver, and gas within the biliary system. Portal vein gas extends to the periphery of the liver shadow, while biliary tract gas remains centrally distributed around the porta hepatis. In biliary tract disease of this nature the common bile duct and the gallbladder, if present, are filled with gas. Gas within the portal vein flows with the blood stream centrifugally and hence to the periphery of the liver, but gas within the biliary tree goes peripherally, only as far as it is permitted by the natural centripetal flow of the bile.—*Samuel G. Henderson, M.D.*

Millar, Douglas M. Tension pneumoperitoneum: postoperative complication. *Brit. J. Surg.*, Jan., 1962, *44*, 394–396. (Address: Senior Surgical Registrar, St. George's Hospital, London, England.)

Tension pneumoperitoneum is a rare postoperative complication. The author reports a case of a 65 year old patient who developed this 17 days after removal of a gangrenous appendix. The presenting symptoms were dyspnea and cyanosis. Roentgenograms demonstrated a massive intra-abdominal collection of gas.

Following insertion of a cannula the gas escaped and did not reform. The gas had no odor.

The author postulates that administration of pitressin tannate to relieve a paralytic ileus may have forced air through an abscess at the appendiceal stump.—*George L. Sackett, Jr., M.D.*

Gynecology and Obstetrics

Dyer, Isadore, and Barclay, David L. Accidental trauma complicating pregnancy and delivery. *Am. J. Obst. & Gynec.*, Apr., 1962, *83*, 907–929. (From: The Department of Obstetrics and Gynecology, Tulane University School of Medicine, New Orleans, La.)

Fifty-three cases of trauma in pregnancy and 23 of preconceptual trauma are reviewed. Auto vehicle accidents accounted for 30 instances of severe maternal trauma. Of these, 12 sustained pelvic fractures which typically involved the pubic rami with disruption of the symphysis pubis and accompanying disruption of the sacroiliac joint. Twelve patients sustained extremity fractures and one a basilar skull fracture. The treatment of fractures was not altered by the presence of pregnancy. In one patient the injury produced a fracture of the fetal skull *in utero*. The infant, following a normal delivery, had no neurologic deficit. Auto vehicle accidents were responsible for 2 maternal and 7 fetal deaths.

Penetrating wounds were observed in 7 patients. These resulted in interruption of pregnancy in every case which involved the gravid uterus. Thirteen falls and 3 severe beatings completed the injuries sustained in pregnancy in the group reviewed.

Blunt abdominal trauma produced the most serious injuries and was responsible for the 2 maternal deaths and 3 fetal deaths. One maternal death was due to a ruptured liver, while in the other a ruptured uterine vein was discovered. The uterus need not be disturbed during surgical exploration for internal abdominal trauma unless necessary for adequate exposure or the presence of direct uterine injuries. A woman may undergo laparotomy and be delivered vaginally without incident 72 hours later.

As a rule, pregnancy is unaffected by severe pelvic fractures. Of 13 cases of pelvic fractures during pregnancy only 3 resulted in interruption of pregnancy. Pelvic fracture prior to pregnancy may, however, alter the mode of delivery. Injury to the sacrococcygeal joint resulting in ankylosis and acute angulation, may compromise the anteroposterior diameter of the pelvic outlet necessitating refracture of the coccyx or abdominal delivery. Of 22 patients who sustained fracture prior to delivery, 8 required abdominal delivery.

Reference is made to the legal aspects of fetal injury *in utero*.—*Francis P. Shea, M.D.*

Skeletal System

Lapidus, Paul W. Epiphysitis of accessory scaphoid—a painful condition of the foot similar to Osgood Schlatter's disease at the knee. *Bull. Hosp. Joint Dis.*, Apr., 1961, *22*, 82–94.

The author's purpose is to call attention to a painful condition of the accessory tarsal scaphoid occurring in adolescence with symptoms resembling Osgood Schlatter's disease. Several theories have been proposed concerning the changes in the tarsal scaphoid and its relationship to flat feet. The author

believes that epiphysitis of the accessory scaphoid is not the same as Köhler's disease of the tarsal scaphoid nor is it a primary factor in the production of flat feet.

Four cases in adolescents with painful feet are described and the accessory scaphoids are demonstrated roentgenographically. All responded to treatment with steroids introduced locally.

Sometimes an accessory scaphoid or an unusually large medial tubercle of the navicular bone projects over the medial portion of the foot and symptoms are produced by mechanical irritation from the shoe.

The fifth case had osteoarthritic changes and pain in a real joint formed between the accessory scaphoid and the navicular tubercle. This case also responded to local steroids.

All four adolescent cases were in females and all had bilateral accessory scaphoids. The left foot only was symptomatic but this was coincidental. All cases responded to local steroid therapy.

The author believes that the etiologic factors operating in Osgood Schlatter's disease are similar to the factors producing the painful accessory scaphoid.—*George A. Kling, M.D.*

Phillips, E. W., Young, Bennett, and Wickstrom, Jack. Legg-Calvé-Perthes disease: the roentgenologic changes with therapy in forty patients. *South. M. J.*, Feb., 1962, *55*, 137–143. (From: The Division of Orthopaedic Surgery, Tulane University School of Medicine, New Orleans, and Shriners' Hospital, Shreveport, La.)

A review of the records of patients with Legg-Calvé-Perthes syndrome, at the Shriners' Hospital of Shreveport, Louisiana, between 1922 and 1955, revealed that only records after 1940 were useful for purposes of comparing the end results of surgical and nonsurgical therapy, and determining the point in the reparative process at which unrestricted weight bearing may be allowed.

Records of 66 children were studied but, because of inadequate data or follow-up in some, only 36 cases with 42 involved hips were selected for final analysis.

Ten hips were treated by surgical epiphysiodesis with only fair results; 15 hips were allowed "limited ambulation" early in the disease with poor results. The rest were permitted nonweight-bearing ambulation with the use of a sling or ischial brace. The results in this group were the best, but the epiphyseal indices did not compare favorably with those reported in the literature treated by recumbency.

No absolute criteria could be formulated as to when weight bearing could be allowed without risk of progression of deformity.—*Lois Cowan Collins, M.D.*

Murphy, Frank P., Dahlin, David C., and Sullivan, C. Roger. Articular synovial chondromatosis. *J. Bone & Joint Surg.*, Jan., 1962, *44A*, 77–86. (From: The Section of Orthopedic Surgery and the Section of Surgical Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minn.)

Thirty two cases of synovial chondromatosis involving joints were treated at the Mayo Clinic from 1910 to 1957. This condition was believed to be quite rare when exacting diagnostic criteria including the findings of metaplastic foci of cartilage in the synovial membrane were required. The most common symptoms and findings were pain, swelling, and limited motion. Other less common findings were limp, stiffness, locking, mass, palpable loose body, thickened synovial membrane, crepitus, and muscle atrophy. The average duration of symptoms was 5.5 years. The joint most frequently involved was the knee (22 cases). Other joints involved were the hip, elbow, ankle, shoulder and wrist.

Of the 32 cases studied, 20 had roentgenographic examination of the involved joint. Numerous small radiopaque masses were present in 13 of the roentgenographed cases.

In 4 cases, only osteoporosis or degenerative disease or both were present; in 3 cases, no abnormality was demonstrated.

Surgical treatment consisting of synovectomy of the involved synovial membrane and removal of loose bodies is considered to be the treatment of choice.—*George A. Miller, M.D.*

Garusi, G. F., and Franchi, B. Pseudocystic images in osteoarthrosis of the hip: radiological stratigraphic study. *Radiol. clin.*, 1962, *31*, 19–38. (Address: Ospedale Policlinico S. Orsola, Istituto del Radio, Bologna, Italy.)

The pseudocystic images discussed are the radiolucent defects frequently seen in the acetabular roof and/or the femoral head of osteoarthrotic hips. These changes, which are the result of osteonecrotic foci secondary to alterations in the bone resulting from abnormal weight-bearing, are an index of the seriousness of the disturbed articular function.

The defects are present in the weight-bearing areas, are present in over 50 per cent of patients with hip arthrosis, are frequently multiple, and occasionally may be demonstrated by laminagraphy.

Eighteen references from the world literature are appended to the article.—*F. B. Markunas, M.D.*

Blood and Lymph System

Thevenet, A., and Vialla, M. Les oblitérations chroniques aorto-iliaques (étude aortographique). (Chronic aorto-iliac obliterations

[aortographic study].) *J. de radiol., d'électrol. et de méd. nucléaire*, Aug.–Sept., 1961, *42*, 447–457. (From: Service central de Radiologie and Clinique de Chirurgie thoracique [Pr E. Nègre] des Hôpitaux de Montpellier, Montpellier, France.)

The importance of demonstration of segmental narrowing or complete obliteration of aorta (distal to the renal arteries) and of the iliac arteries lies in the fact of preventing thrombosis or restoring circulation by surgery (endarterectomy, arterial graft, anastomosis). Serial angiography of upper pelvic region is set at the rate of one exposure per second for 6 exposures, whereas femoro-popliteal angiographic series are set for 10 exposures, one every 2 seconds. Such timing has been found optimal for demonstration of small atheromatous filling defects.

Four cases of complete aortic obliteration (thrombosis) immediately distal to the renal arteries and 19 cases of incomplete obstruction (funnel shaped or segmental narrowing of lumen) were observed by the authors. The collateral circulation is often established through the visceral vessels. If obliteration is proximal to the inferior mesenteric artery, then the middle colic branch of the superior mesenteric artery will conduct the circulation to the left colic artery and via the hemorrhoid arteries to the hypogastric artery. In case of obliteration immediately distal to the inferior mesenteric artery, the collateral circulation is directly through the middle and inferior hemorrhoid branches of the hypogastric atrery. All these collateral vessels are enlarged three times their normal size. Parietal vessels, as the lumbar, iliac circumflex, external ilio-lumbar and gluteal branches of hypogastric arteries also contribute to the collateral circulation.

Eleven cases of complete unilateral iliac obliterations and 34 cases of incomplete stenotic changes (16 right and 18 left of which 6 were bilateral) were observed. The collateral circulation is again through the visceral and parietal vessels. In case of unilateral involvement, branches of the opposite hypogastric artery constitute the more important collateral circulation. Eight cases of segmental complete obstruction (5 right, 3 left and 1 bilateral) and 21 cases of incomplete obstruction (9 right, 12 left and 7 bilateral) of the external iliac arteries were observed. The main collateral circulation is established through the hypogastric artery and its branches. Ten cases of segmental complete obstruction (3 right and 7 left) and 15 cases of incomplete obstruction (8 right, 7 left and 2 bilateral) of the internal iliac arteries were demonstrated. Collateral circulation was the same as above.

Femoro-popliteal lesions were observed very frequently (80 per cent) in association with both complete and incomplete obstruction of aorta and iliac arteries. These peripheral lesions were bilateral in 70 per cent of cases.—*J. N. Sarian, M.D.*

Rösch, J. Splenoportographie im Kindesalter. (Splenoportography in children.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Jan., 1962, *96*, 61–75. (Address: Dr. J. Rösch, V Borcové 2, Praha 6, Brevnov, Czechoslovakia.)

Splenoportography in adults is a well established procedure; in children, however, it is very little used. The study aids the surgeon, the gastroenterologist, hematologist, and pediatrician. It helps to determine portal hypertension, the nature of epigastric masses and pancreatic disease, and the causes of hepatosplenomegaly, intestinal hemorrhage, and ascites.

Twenty-seven children were studied with a total of 32 examinations. Two of these had no splenomegaly. The age ranged from 14 years to 7 months with an average age of 7.3 years.

The cases were divided into 6 groups as follows: (1) Normals (2 cases). (2) Systemic splenomegaly due to malignant lymphogranulomatosis (2 cases). (3) Splenomegaly with hematemesis and collateral circulation due to congenital portal vein occlusion, (6 cases). In 4 of these, the occlusion and collateral circulation were well seen, in 2 there was nonfilling of the portal vein. (4) Splenomegaly due to portal vein thrombosis (5 cases). (5) Hepatitis, chronic type (3 cases) and posthepatitic changes for determination of liver damage and portal vein circulation (4 cases). There was multiple branching of portal vein within both lobes of the liver, but no evidence of collateral circulation. (6) Cirrhosis of liver with hematologic findings of hypersplenism (6 cases). There was deformity and poor branching of small and medium sized portal vein branches and collateral circulation.

In children no cooperation can be expected. Therefore, the examination has to be done under full anesthesia with induced full respiratory arrest. There was no untoward reaction. The examination was successful in 26 children and a partial failure only in one.

The procedure is contraindicated in little children without splenomegaly. When the spleen is small, it is difficult to place the needle correctly, even under fluoroscopic control. The filling of the portal vein and of the collaterals occurs much more rapidly than in adults. Thus, serial filming has to start at the beginning of the injection. The roentgen findings do not differ much from those in adults. Only the collateral circulation is more abundant. In the subhepatic area it may even simulate a cavernous hemangioma.

Splenoportography in children is valuable for hepatosplenomegaly with intestinal hemorrhage, ascites, collateral circulation in the wall of the abdomen and chest, and tumors of the epigastrium. In splenomegaly, it helps to find the cause as well as the relation to a large liver and the changes in splenoportal circulation. It aids the surgeon in planning an operation. In hepatomegaly, it shows the character and degree of liver disease and reveals secondary

changes of the portal vein. In intestinal hemorrhage, it discloses the relation of the portal vein to the collateral circulation. When the cause is established, proper therapy can be instituted. In epigastric tumors, splenoportography serves only as an auxiliary method.—*Ernest Kraft, M.D.*

Marchal, Georges, Bernard, Jacques, Arvay, N., Bilski-Pasquier, G., Ecoiffier, J., and Picard, J. D. (Paris, France.) La phlébographie dans le dépistage des adénopathies profondes; son intérêt diagnostique et thérapeutique dans les hémopathies malignes. (Phlebography in the detection of deep adenopathy; its diagnostic and therapeutic significance in malignant hemopathies.) *Presse méd.*, Dec., 1961, *56*, 2586-2588.

The intimate contact between lymph nodes and main venous trunks, particularly the iliac and caval ones, and the ease with which the veins are compressed or deviated, explain how phlebography helps detect deep lymph node masses that may be difficult to localize clinically.

Phlebography, which may be repeated without appreciable danger to the patient, increases the safety and efficacy of radiation therapy in lymphadenopathies due to the precision of the topographic data obtained.

A total of 80 ml. of contrast medium is injected simultaneously into both femoral veins, utilizing the Valsalva maneuver, which results in a good demonstration of the iliac veins and inferior vena cava.

Normal compression of the proximal portion of the iliac veins by the corresponding arteries must be recognized. Compression, deviation and blockage of the veins usually indicate the site of lymph node masses or tumor extension.—*Charles M. Nice, Jr., M.D., Ph.D.*

RADIATION THERAPY

Bosio, L., and Isola, A. La radioepidermolisi; ripara solo con la sopravvivenza di elementi epidermici o con il loro trapianto precoce. (Radioepidermolysis; repair only through the survival of the epidermal elements or by early grafting.) *Radiol. med.*, Dec., 1961, *47*, 1121–1136. (Address: Via Anelli 9, Milano, Italy.)

It is well known that in some cases of radioepidermolysis there is at times a rapid recovery of the epidermis, while in other cases there is a sudden worsening of the local conditions with rapid passage of the process into ulcerative radiation dermatitis.

The authors feel that the explanation of this different behavior is based on the changes which follow epidermolysis and occur in the epidermis and the dermis. Therefore, the prognosis of the evolution of the lesion is related to the extension in depth of the cellular epithelial damage.

If the whole epidermis is not destroyed by the radiation the remaining islands of epidermis will be sufficient to regenerate the epidermal layers. However, if the islands of epidermis are very few the process of repair will only be from the dermis and the end result will be sclerotic scar.

Dependent on the intensity of the radiation, if the blisters arise between the epidermal layers, the formation of new epithelium will occur more rapidly; if instead they occur between the epidermis and the dermis, the formation of new epithelium will be possible only in lesions which are not particularly large, and the new cells will originate from the normal epithelium situated at the edges of the area involved. However, even in larger lesions, if there are central islands of normal epithelium, the process of repair begins also from these islands and progresses toward the periphery.

These different reactions of the epidermis to irradiation are related to the different intensity of the dose received by the various layers of the skin and also to the different sensitivity of the cells. This nonuniformity of reaction of the surface of the skin to a homogeneous stimulus could be explained by the hypothesis introduced by Aiello. This author suggests that the various organs of the human body are formed by numerous small entities such as the lobules in the liver, the follicles, the glandular islands, etc. These formations are characterized by an alternating and rhythmic function such as in the nephron.

As regards the skin, we should accept the hypothesis that biologically the epidermis is made up of "dermatons" which, when irradiated and not destroyed or at least not deeply affected, can resume their activity and reform the whole epidermis.

In radiation dermatitis and in particular in radioepidermolysis, following the usual radiation damage, the nerve endings are completely unprotected and therefore severe pain ensues. In these cases the authors use very fine sheets of silver of the same type as used in gilding. The fine sheets adhere to the area in which the epidermis is absent and protect it. These sheets of silver also have a beneficial effect on the process of repair. This process can be enhanced by the use of a cream containing sulfanilamides or antibiotics. Interestingly, the silver sheets remain intact in the areas where there is already new epiphelium but are destroyed where the process of repair is not taking place. One must assume that in the areas without epithelial cells, electrobiologic phenomena occur which produce at the same time protection, disinfection, and act as a stimulus to the process of repair. A new sheet of silver is placed over the areas in which the old one is dissolved and the wound is cleansed only every 3 or 4 days.

Finally, the authors recommend that, when there

is destruction of the epidermis and dermis following irradiations, the epidermal layers should immediately be repaired by an early grafting. This is considered to be the first definite indication of surgical intervention in lesions produced by irradiation. This grafting should begin after the appearance of the blisters, in order to obtain a repair almost *ad integrum*. Furthermore, the changes in the dermis will also be reduced without any deep scarring.

Two cases are described and illustrated with demonstrative colored photographs.—*A. F. Govoni, M.D.*

Herman, Murray, and Levy, Edward S. Carotid sinus syncope treated with roentgen therapy. *A.M.A. Arch. Int. Med.*, Mar., 1962, *109*, 287–289. (Address: Ozaukee Medical Center, 229 S. Main Street, Thiensville, Wis.)

The authors present a case report of a patient with carotid sinus syncope who had been symptomatic and undiagnosed for 4 years. Treatment with atropine and isuprel was soon discontinued because of toxic reactions. Roentgen therapy consisting of three exposures of 250 r in air, 50 cm. skin target distance and a 5×5 cm. field to the right carotid sinus was then given and repeated one month later because of recurrent syncope. Following this the patient remained asymptomatic to the time of this report (16 months).

A brief discussion of the three types of carotid sinus syncope (vagal, depressor and cerebral) and their treatments is given.

The authors conclude that a patient who does not respond to drug therapy should be given a course of irradiation to the carotid sinus before surgical denervation of the carotid sinus is attempted.—*Francis P. Shea, M.D.*

Kolár, Jaromír, Vrabec, Radko, and Zdenek, Král. Strahlenkrebs nach Hämangiombehandlung. (Radiation cancer after treatment of hemangiomas.) *Strahlentherapie*, Jan., 1962, *117*, 247–255. (Address: Radiologische Klinik, U Nemocinice 2, Praha 2, Czechoslovakia.)

Chronic, protracted exposure to radiation over a long time is more likely to be the cause of radiation cancer than is an acute, single large dose. Thus, in the past, because of inadequate protective measures, physicians aud other radiation workers were the usual victims of radiation cancer. Nowadays however, therapeutic radiation is usually to blame for radiation cancer. Indeed, the majority of patients with radiation cancer were treated (usually from 4–10 years earlier) for benign conditions.

The authors report 5 patients who had radiation therapy for their hemangiomas in childhood and then developed, successively, chronic skin damage and radiation carcinoma in the treated areas. Four of these patients had been treated with radium, one with roentgen rays. In each instance, radical excision of the involved skin and underlying tissues has left the patient well and without evidence of carcinoma. —*Henry G. Moehring, M.D.*

Magno, L. Sul valore semeiotico dell'elettroforesi delle proteine del siero nelle malattie neoplastiche con particolare riguardo ai pazienti sottoposti a radioterapia. (On the semeiotic value of electrophoresis of the serum proteins in neoplastic diseases, with particular emphasis on patients treated by radiotherapy.) *Radiol. med.*, Dec., 1961, *47*, 1191–1202. (Address: Via San Rocchino 24, Brescia, Italy.)

One hundred and four patients treated by radiotherapy were studied by the author in order to reach a more definite conclusion on the possible relationship between electrophoretic patterns and neoplastic diseases. Two hundred fifty electrophoretic determinations were performed in 50 patients affected by lymphoblastomas and 54 by malignant epithelial tumors.

From the data obtained, the following conclusions are drawn: (1) there is no relationship between the type of the tumor (at least the ones studied by the author) and the electrophoretic patterns; (2) the more frequent changes in the electrophoretic patterns of the serum proteins, in cases of lymphoblastomas, are reductions in the albumins and an increase in the alfa 2 and gamma globulins; (3) there is no constant and significant relationship between the stage of the tumor, or the changes in the tumor following radiotherapy, and the electrophoretic patterns of the serum proteins; (4) electrophoretic determinations of the serum proteins in the patients with neoplastic diseases provide the clinician and the radiologist with very definite and precious information regarding the general condition of the patient.

It is recommended that cancer patients should have frequent electrophoretic determinations of the serum proteins in order to correct with adequate therapy a protein imbalance, whenever the tumor itself and the changes secondary to radiotherapy tend to alter the normal proteinemic values.—*A. F. Govoni, M.D.*

Thackray, A. C. Mucous gland tumours. *Clin. Radiol.*, Oct., 1961, *12*, 241–245. (From: Bland Sutton Institute of Pathology, The Middlesex Hospital, London, W.1, England.)

The author states that mucous gland tumors may arise in connection with any of the three main groups of glands: (a) the major salivary glands, (b) the minor salivary glands found in the mucosa of the

cheeks and lips, in the tongue, peritonsillar region and palate, and (c) the mucous glands of the respiratory tract from the nose down to the bronchi. The tumors arising from the minor salivary glands and mucous glands of the respiratory tract are collectively known as mucous gland tumors, presenting as affections of the mucous membrane. The four histologic types of tumor include the mixed parotid type, the cylindromatous type, muco-epidermoid tumors and mucous gland carcinoma. These four types of tumor differ in their behavior and response to treatment.

The mixed parotid type tumors can usually be enucleated easily, but are liable to eventual recurrence because of fragments of tumor left behind at enucleation. Not over 2 or 3 per cent of this type of tumor become malignant. The cylindromatous type of mucous gland tumor, known variously as "cylindroma," "basilioma" and "adenoid cystic carcinoma," infiltrates far into the adjoining structures and is rarely cured surgically, but may have a long course of 10 to 15 years or more before death ensues. Some 5 to 10 per cent of these tumors change to a poorly differentiated rapidly growing carcinoma. Muco-epidermoid tumors are not frequent, but are regarded as all in varying degrees malignant. Mucous gland carcinomas invade rapidly and metastasize early, with a uniformly bad prognosis.—*Samuel G. Henderson, M.D.*

Wilson, C. P. Extra parotid mucous gland tumours. *Clin. Radiol.*, Oct., 1961, *12*, 246–250. (From: The Middlesex Hospital, London, W. 1, England.)

The extra parotid tumors are notable because of their wide area of occurrence, their unexpectedness in a given location, and the unpredictability of their behavior. The result of surgery alone in salivary tumors of all types where there is easy accessibility with adequate uninvolved surrounding tissue is good, but not so with difficult accessibility and insufficient margin of adjacent normal tissues, particularly in cylindroma or definitely malignant tumors. In these cases supervoltage therapy is the first choice of treatment.

In the benign, mixed parotid type radiotherapy should be used as the primary form of treatment in all cases in which complete removal with an adequate margin of healthy tissue is considered impossible, with surgery reserved for subsequent use if any persistent growth remains. While many of the extra parotid mucous gland tumors are radioresistant, yet where surgery is likely to be inadequate or to involve severe mutilation preliminary radiotherapy is considered advisable, because it is not at present possible to decide beforehand whether a tumor will be radioresistant.—*Samuel G. Henderson, M.D.*

Pattinson, J. N. Mucous gland tumours of the nose and throat: radiological appearances. *Clin. Radiol.*, Oct., 1961, *12*, 251–258. (From: Radiodiagnostic Department, The Middlesex Hospital, London, W.1, England.)

The author reviewed the roentgenograms of 31 cases of mucous gland tumors of the nose and throat. Roentgenologic changes included bone destruction, bone expansion and the presence of a tumor mass. The roentgenologic appearances can be fairly well correlated with the pathologic and clinical features. The presence of a soft tissue mass may be a prominent feature in the mixed parotid type tumor which tends to form a rounded and bulky lump. In the case of a cylindroma the mass is often flat, and, if confined to the hard palate or nasopharynx, may be inconspicuous. A tumor encroaching on the air-way of the nasal accessory sinuses or of the trachea is usually demonstrable, but in the sinuses it is often difficult to roentgenologically differentiate the tumor mass from chronic inflammatory swelling of the mucosa and retained secretions. Bone destruction is a common early finding in mucous gland tumors of the nose and throat, particularly if the tumor originates in the hard palate, or in one of the nasal accessory sinuses. Thinning and expansion of bone is a common finding, and may accompany areas of bone destruction—most commonly seen in the slow growing tumors. In one patient there was roentgenologic evidence of dense and irregular calcification in a benign mixed tumor, simulating the appearance often seen in cartilaginous tumors.

In malignant tumors distant metastases may occur in the lymph nodes, brain, liver, bone, lungs and pleura. The chest should always be included in the initial roentgenologic investigation, and also in the routine follow-up of all cases of mucous gland tumors.—*Samuel G. Henderson, M.D.*

Snelling, Margaret D. Results of treatment of mucous gland tumours of the nose and throat. *Clin. Radiol.*, Oct., 1961, *12*, 259–268. (From: Meyerstein Institute of Radiotherapy, The Middlesex Hospital, London, W.1, England.)

It is difficult to assess the results of treatment of the mucous gland tumors since the recurrence is late, on the average mixed parotid type tumors recurring 5 years, and cylindromas 3 years after treatment. Of 66 cases treated before 1955, 22 have remained without recurrence for periods varying from 5 to 32 years, but 31 are known to have recurred and 13 were lost to follow-up. In the mixed parotid type tumors 15 out of 31 treated are known to be without recurrence, while only 5 out of 29 cylindromas have remained well.

Tumors of the palate form the largest and most important group in this series, 31 of the entire group of 87 having had tumors in this site. These included 17 of 35 mixed parotid type tumors and 11 of 43 cylindromas. The number of cylindromas has in-

creased greatly in recent years. Also in the group of tumors of the palate there were 3 adenocarcinomas and one muco-epidermoid tumor. Repeated treatment of recurrences in these tumors either with surgery or with radiotherapy, or with a combination of the two is well worth while, since, even if complete cure is not achieved, the patient may be enabled to live many years without serious symptoms.

Peritonsillar tumors are soon noticed by the patient, and prognosis is improved by the prevalence of mixed parotid type tumors. In tumors of the maxillary antrum and ethmoids the diagnosis becomes more difficult, and the prognosis is made worse by the increasing frequency of cylindromas, and by the delay in diagnosis. In this group of patients the main line of treatment must be radiotherapy, with later surgery where indicated.

Radiotherapy is of the greatest importance in the treatment of infiltrating cylindromas, but is also of value in case of mixed parotid type tumors in which their site or extent makes treatment by surgery alone unsuitable. The main feature of the tumors is their infiltrating nature which means that a large volume of surrounding tissue must be treated. In cases of carcinoma of the antrum treatment must include the orbit, nasal sinuses, ethmoid air cells, sphenoid air sinuses, nasal cavity and palate. Because of the infiltration of bone and cartilage and because of the radioresistance of the tumor, supervoltage irradiation is used with high dosage in the order of 6,000 to 6,500 rads over 6 to 8 weeks, each case being planned individually.—*Samuel G. Henderson, M.D.*

RADIOISOTOPES

Blau, Monte, and Bender, Merrill A. Radiomercury (Hg^{203}) labeled neohydrin: a new agent for brain tumor localization. *J. Nuclear Med.*, Mar., 1962, *3*, 83–93. (From: The Department of Nuclear Medicine, Roswell Park Memorial Institute, Buffalo, N. Y.)

Radiomercury (Hg^{203}) has been proposed by the Oak Ridge group as an ideal tracer for gamma-ray scintillation scanning techniques. Its physical properties are interesting, for it has a half life of 45.8 days, and its emissions are a beta particle of 0.21 mev. and a single gamma ray of 0.28 mev. Impressed by the fact that the single gamma ray of relatively low energy would be easier to collimate for scanning purposes, and thus might afford more accurate localization in the scanning of brain tumors, the authors searched for a mercury-containing compound which might be synthesized with Hg^{203}, and settled upon neohydrin, a mercurial diuretic. Neohydrin displays a distinct advantage as a tracer when compared with radioactive iodinated human serum albumin (HSA) in that its biologic half life is considerably shorter. Half of the excretion of neohydrin is accomplished in 8 hours, and despite the longer half life of the mercury tracer the authors estimate that the total dose to the patient in a brain tumor scan will be of the order of 290 mrad as compared to 700 mrad delivered by a dose of 5 μc/kg. of I^{131} human serum albumin. Selective retention of neohydrin by the kidneys may be significantly reduced by administering 1 cc. of mercurhydrin, another mercurial diuretic, on the day prior to scanning. Even so, the dose to the kidneys with an average scan dose of Hg^{203} neohydrin of 10 μc/kg. will be of the order of 20 to 25 rad.

The tracer dose was administered 4 to 5 hours before scanning and the authors employed their well-known photoscanning apparatus which includes a 61-hole, 3-inch lead focusing collimator and a 3-inch×2-inch thallium-activated sodium iodide crystal. One hundred patients who were thought to have brain tumors were scanned with both Hg^{203} neohydrin and I^{131} human serum albumin and several comparison scans are shown. The accuracy of the scan method for localization of brain tumors is said to be about 85 per cent in the hands of the authors, and somewhat better definition is obtained with Hg^{203} neohydrin in about one-quarter to one-third of all cases, when compared with I^{131} HSA. In the words of the authors the resultant improvement in visualization of tumors with this new tracer substance is significant, but not dramatic. It does, however, constitute an interesting new development.—*Frederick F. Bonte, M.D.*

Freiman, Henry D., Cohn, Edwin M., and Sklaroff, David M. The inadequacy of radio-iodinated (I^{131}) iodipamide as a liver function test. *J. Nuclear Med.*, Jan., 1962, *3*, 63–66. (From: The Isotope Division of the Department of Radiology, Albert Einstein Medical Center, Philadelphia, Pa.)

Previous investigators have reported the value of clearance of radioactive iodipamide (cholografin) from the blood and its excretion in the urine as a test of liver function.

The present authors studied 32 patients, 14 of whom had either hepatocellular disease or obstructive biliary disease. Blood levels of radioactivity and recovery of radioactivity in the urine were determined after administration of 0.5 μc of I^{131} labeled iodipamide per kg. injected intravenously. This dose amounted to approximately 0.25 mg. of iodipamide.

Fifty per cent of the radioactivity was recovered from the blood in patients without hepatic disease in 4.8 hours. For patients with hepatocellular disease and hepatic obstructive disease, the times were 6.8 and 6.0 hours respectively. Statistical analysis (method of least squares) indicated no differences between the three groups. Urine levels also revealed no significant differences. Thus, radioactive iodip-

amide had no value as a liver function test in the dosage used.

It is generally recognized that iodipamide is removed more slowly from the blood stream of patients with liver disease. In the routine use of iodipamide for cholangiography, 4 to 8 gm. of the drug is used, while 0.25 mg. of radioactive iodipamide is employed. This may explain the variance in the authors' results; perhaps the 0.25 mg. is not a great enough dose for the diseased liver because of the inherent liver reserve usually present in most patients with hepatic disease.—*William K. Littman, M.D.*

Karras, Bill Gust, and Moss, William T. Radioactive gold in the control of malignant serous effusions. *Quart. Bull. Northwestern Univ. M. School*, Spring, 1962, *36*, 57–59. (From: The Department of Radiology, Northwestern University Medical School, and the Department of Radiation Therapy, Chicago Wesley Memorial Hospital, Chicago, Ill.)

This is a review from the Northwestern University of the use of radioactive gold in the control of malignant effusion.

A total of 56 cases suitable for study are presented; 37 with effusion in the pleural cavity and 19 with effusion in the abdominal cavity. Successful control, for 6 weeks or more, was obtained in 65 per cent of the pleural series and 25 per cent of the abdominal series. Doses of about 100 mc were used in the chest and 150 mc in the abdomen.

The disadvantages of Au^{198} are discussed and it is concluded that this is still the agent of choice in controlling malignant effusions.—*Henry J. Klos, M.D.*

Ariel, Irving M. Five-year cure of a primary malignant melanoma of the vagina by local radioactive isotope therapy. *Am. J. Obst. & Gynec.*, Aug., 1961, *82*, 405–407. (Address: 139 East 36th Street, New York, N. Y.)

The author reports a rare melanoma of the vagina with an even more rare 5 year survival without residual, the result being attributed to the interstitial and topical use of P^{32}.

This 47 year old woman had a large, fungating, ulcerating, and foul black mass in the upper vagina. With the hope of palliation, 8 mc of radioactive chromic phosphate (P^{32}) plus 10 mg. of thiotepa was injected into the tumor which became less foul. One month later 10 one mc gold radon seeds were implanted into the tumor which began to shrink. Six months later 6 mc of the P^{32} was injected into the residual mass and finally another 5 mc was injected after 2 months leading to complete disappearance of the mass. This treatment covered a period of 10 months.

The posterior vaginal wall was black due to melanoma infiltration which remained after the upper vaginal tumor disappeared. Eight mc of P^{32} were saturated into white blotting paper and placed against the posterior vaginal wall for 96 hours giving an estimated dose of 40,000 rads. A brisk erythema appeared and the black began to clear in 2 weeks and was virtually gone in 3 months.

She is alive 5 years after beginning of therapy and 4 years 1 month after its completion.—*Henry J. Klos, M.D.*

Ariel, Irving M. Radioactive isotope therapy for ovarian carcinoma: subsequent pregnancy and intra-abdominal radioactive isotope therapy during pregnancy. *J.A.M.A.*, July, 1961, *176*, 1117–1119. (Address: 139 East 36th Street, New York, N.Y.)

This report details the case of a 22 year old woman with abdominal carcinomatosis who became pregnant 6 months after treatment with intraperitoneal radioactive gold (Au^{198}) and radioactive chromic phosphate (P^{32}) and was treated again with the P^{32} one month after the unsuspected conception and then was delivered of a normal baby.

At the time of the original surgery a large papillary adenocarcinoma of the left ovary was removed. The peritoneum was studded with tumor masses, the omentum was infiltrated and 8 liters of fluid were present. She was given 75 mc of Au^{198} and 20 mc of P^{32}, the estimated dose to the peritoneum being 66,700 rads beta equivalent and 4,000 rads gamma from the gold.

Six months later she missed a period (assumed to be an effect of the radiation) and was given another 20 mc of P^{32}. Subsequent roentgen examination of the enlarging abdominal mass demonstrated a fetal skeleton. It was estimated that the patient was in the first month of gestation when the P^{32} was given.

At term, a normal baby was delivered by cesarean section. There were numerous areas of scarring throughout the peritoneum but no evidence of tumor.

The author implies that had Au^{198} been used the second time, radiation effects might have been detected in the fetus.—*Henry J. Klos, M.D.*

Greenberg, Joseph, Sawitsky, Arthur, Dudley, H. C., Levy, Robert N., and Rai, Kanti R. Therapy of polycythemia vera with radioyttrium (Y-90). *J. Nuclear Med.*, Jan., 1962, *3*, 18–25. (From: The Divisions of Nuclear Medicine and Hematology, The Long Island Jewish Hospital, New Hyde Park, New York, N.Y.)

Radioactive yttrium (Y^{90}) is a 2.18 mev. pure beta emitter with a half life of 61 hours. It has a strong affinity for chelating agents, and because of this property, it is possible to achieve significant selective localization of Y^{90} in a number of organs in man

including bone, marrow, liver, spleen, lymph nodes, and gastric mucosa. Thus, a theoretic advantage of Y^{90} over P^{32} is its shorter half life (61 hours compared to 14.3 days) and preferential localization of chelated (with N'hydroxy ethylenediamine triacetic acid [Ed-ol]) Y^{90} in bone. This makes possible a larger dose of internal radiation to the tumor site with minimal systemic effects.

Nine patients have been treated by the authors. Eight were followed from 5 to 17 months. At the time of diagnosis the red blood cell counts ranged from 7 to 10.5 million per cu. mm., hemoglobin from 17 to 23.5 gm. per cent and hematocrit from 56 to 79 per cent. The white blood cell counts varied from 10,000 to 23,000 per cu. mm., and the platelets from 0.5 to over 3.0 million per cu. mm. Six of the patients had received previous P^{32} treatment.

Chelated Y^{90} was administered intravenously as a single dose varying from 0.09 mc/kg. to 0.25 mc/kg. Urine was collected over 72 hours. The amount of Y^{90} retained varied from 69 to 93 per cent of the given dose with an average of 84 per cent. The actual dose delivered varied from 0.09 mc/kg. to 0.23 mc/kg.

Eight patients showed a fall in hemoglobin and hematocrit of 2 to 6 gm. per cent and 12 to 23 per cent respectively. The red blood cell counts fell 1.5 to 4 million per cu. mm. Maximum fall occurred at about 3 months after therapy. The leukocytes fell to levels of 3,000 to 1,300 per cu. mm. in 6 patients; the maximum decline being 3 to 8 weeks after therapy. No infection occurred during the period of leukopenia. Of the 7 patients in whom erythroid components fell below normal levels, 5 have returned to and stayed at essentially normal levels.

All 9 patients have shown a good response 5 to 17 months after a single dose treatment, both as shown by the blood picture and symptoms response. Two patients treated 16 and 9 months ago, may be going into a relapse. Toxicity was limited to transient petechiae and epistaxis. The intravenous administration of a chelate such as Ca-EDTA promotes clearance of Y^{90} by the kidneys should too high a dose level be established.—*William K. Littman, M.D.*

Cassen, B. Multicrystal large well counters. *J. Nuclear Med.*, Mar., 1962, *3*, 128–137. (From: The Laboratory of Nuclear Medicine and Radiation Biology of the Department of Biophysics and Nuclear Medicine, School of Medicine, University of California at Los Angeles, Calif.)

Well counters for samples of relatively large volume, 20 ml. or more, commonly take the form of liquid or plastic scintillation counters in which the volume of the scintillator is relatively large as is the amount of shielding required. The author has approached this problem in an ingenious manner by constructing the equivalent of a large crystal well as follows: a cylinder of lucite of inside length $6\frac{1}{2}$ inches and diameter $5\frac{3}{4}$ inches was constructed, with a well insert of $2\frac{1}{8}$ inch diameter. The space inside the cylinder was filled with 10 kg. of irregular pieces of thallium-activated sodium iodide crystal. The interstices between the crystal fragments were filled with a low viscosity silicone oil of relatively low refractive index. Metallic sodium was added as a dehydrating and deoxidizing agent. The cylinder itself was enclosed in a loose-fitting metal shield, and the space between cylinder and shield was filled with aluminum oxide powder. Two 5-inch photomultiplier tubes were employed, one approximated to each of the flat faces of the cylinder. The phototubes were electrically in parallel so that their simultaneous pulses added. A 2-inch thick lead shield surrounded the cylinder and photomultiplier tubes.

The instrument has a measured background of 43 c/sec., and tests with calibrated mock iodine sources indicate a counting efficiency of about 70 to 80 per cent. Activities of more than 0.2 μc cannot be counted satisfactorily. Although excellent as a large-sample well counter for small quantities of radioactivity, the instrument has not exhibited good spectrometric performance. The author suspects that the symmetric cubic shape of most of the crystal fragments tends to produce internal optical absorption, and is now testing asymmetric pieces of sodium iodide crystal to determine whether optical and radiospectrometric efficiency may be increased in this manner.—*Frederick J. Bonte, M.D.*

Sutro, Charles J. Changes in the synovial tissues of the knees of rabbits following intra-articular injection of thorium (thorotrast). *Bull. Hosp. Joint Dis.*, Apr., 1961, *22*, 39–42.

Roentgenographic examination of the joint spaces has been accepted by many clinics. Thorotrast is not generally used for this. The author wished to study the pathologic reactions in the tissues of rabbit knees following intra-articular injection of colloidal thorium dioxide (thorotrast).

The method employed was the introduction of 2 cc. of thorotrast into the right knee of 8 adult rabbits. In 4 of the rabbits the right femoral articular cartilage was irritated by needle abrasion prior to thorotrast injection. The animals were sacrificed at intervals and the structures studied.

It was found that thorotrast injected into the joint cavity is rapidly taken up by the outer layer of synovial cells and is retained in the subsynovial tissues. Irritative proliferative synovitis and focal necrosis of capsular tissue occurred. The artificially produced cartilage defects healed with newly formed connective tissue which contained radiopaque and radioactive material.

Further experimental work is believed necessary to ascertain whether healing of cartilage defects can

be measured by uptake of radioactive particles. Thorotrast is too toxic an agent for this purpose in man.—*George A. Kling, M.D.*

MISCELLANEOUS

Hovnanian, H. Philip, Longo, John S., Brand, Peter B., Brennan, Timothy A., and Bower, Arthur J. (Wilmington, Mass.) Electro-optic monitor and fluoroscope. *J. Am. Dent. A.*, Mar., 1962, *64*, 323–328.

Closed-circuit television is of great value as a teaching aid in the dental profession, but with standard techniques only the anterior portion of the oral cavity can be viewed satisfactorily. Since the smallest available television camera is too large to insert into the mouth the authors have developed a technique of televising with fiber optics. The functioning principle relies on the conduction of light along a transparent dielectric fiber by means of multiple internal reflections. The fiber bundle is one-half inch in diameter, and is composed of approximately 10,000 individually coated fibers, each .002 inches in diameter. Each fiber isolates a part of the image and conveys it from the small intra-oral probe to the television camera, a distance of one meter. The fiber optic bundle is flexible but the bundle ends are matched so that they occupy the same geometric position. This characteristic provides mechanical flexibility without image distortion. With this system the dentist can demonstrate operative procedures anywhere within the oral cavity.

The authors have also made an intra-oral fluoroscope by replacing the optics of the probe with a thin layer of roentgen-ray-sensitive fluorescent compound. The fluoroscopic image can be seen on a television monitor by a group of students.—*J. L. Williams, M.D.*

Fukuda, Masashi, Sugahara, Tsutomu, and Hashimoto, Tetsuaki. Reliability of film badge method and pocket dosimeters for personnel monitoring. *Strahlentherapie*, Dec., 1961, *116*, 638–645. (From: Department of Radiology, Kyoto University, School of Medicine, Kyoto, Japan.)

The authors' experience indicates that film badges should be used to determine long term accumulation (2–13 weeks) of radiation exposure, and pocket chambers for daily control of high dose irradiation.—*Henry G. Moehring, M.D.*

Hayakawa, Junichiro, Tsuchiya, Takehiko, and Sugahara, Tsutomu. Protective effect of mercazole (1-methyl 2-mercaptoimidazole) against single whole-body irradiations in mice. *Strahlentherapie*, Nov., 1961, *116*, 415–419. (From: Division of Radiation Hazards, National Institute of Radiological Sciences, Chiba, Japan.)

Two inbred strains of mice (RF and C57BL/6) were exposed to near-lethal doses of whole body irradiation. Approximately half of the 357 male mice served as controls and received tap water to drink. The "treated" group received 0.05 per cent mercazole (1-methyl 2-mercaptoimidazole) in their drinking water for a week before being irradiated. The 30 day survival was significantly increased in the treated group of RF strain mice, but not in the other strain.

The authors suggest that this difference in protection against the effects of radiation between the two strains might be the result of: (1) difference in the antithyroid effect of mercazole in the two strains, or (2) perhaps the radiosensitivity of the RF strain is relatively high and is depressed by the mercazole.—*Henry G. Moehring, M.D.*

Hammer-Jacobsen, Erling. Congenital malformations induced by radiation: a brief survey of the literature. *Strahlentherapie*, Sept., 1961, *116*, 152–158. (From: The Radiological Department, University Hospital of Copenhagen, Righospitalet, Copenhagen, Denmark.)

The author's conclusion from this "brief survey of the literature" is as follows:

(1) There seems to be general agreement that irradiation during the first half of the gestation period may cause congenital malformations and that the incidence is increased on increasing the doses. On the other hand, there seem to be no definite facts to rely on as regards lower threshold doses or as to the nature of dose effect graphs. Neither are researchers agreed upon the most radiosensitive phases.

(2) It will presumably be necessary to carry out several animal experiments with doses ranging from about 1 r to 5 r and to follow-up a great number of children who have been irradiated *in utero* with low doses.

For the present, roentgenographic examination of the abdomen should, whenever possible, not be performed during the first 4 months of pregnancy.—*Henry G. Moehring, M.D.*



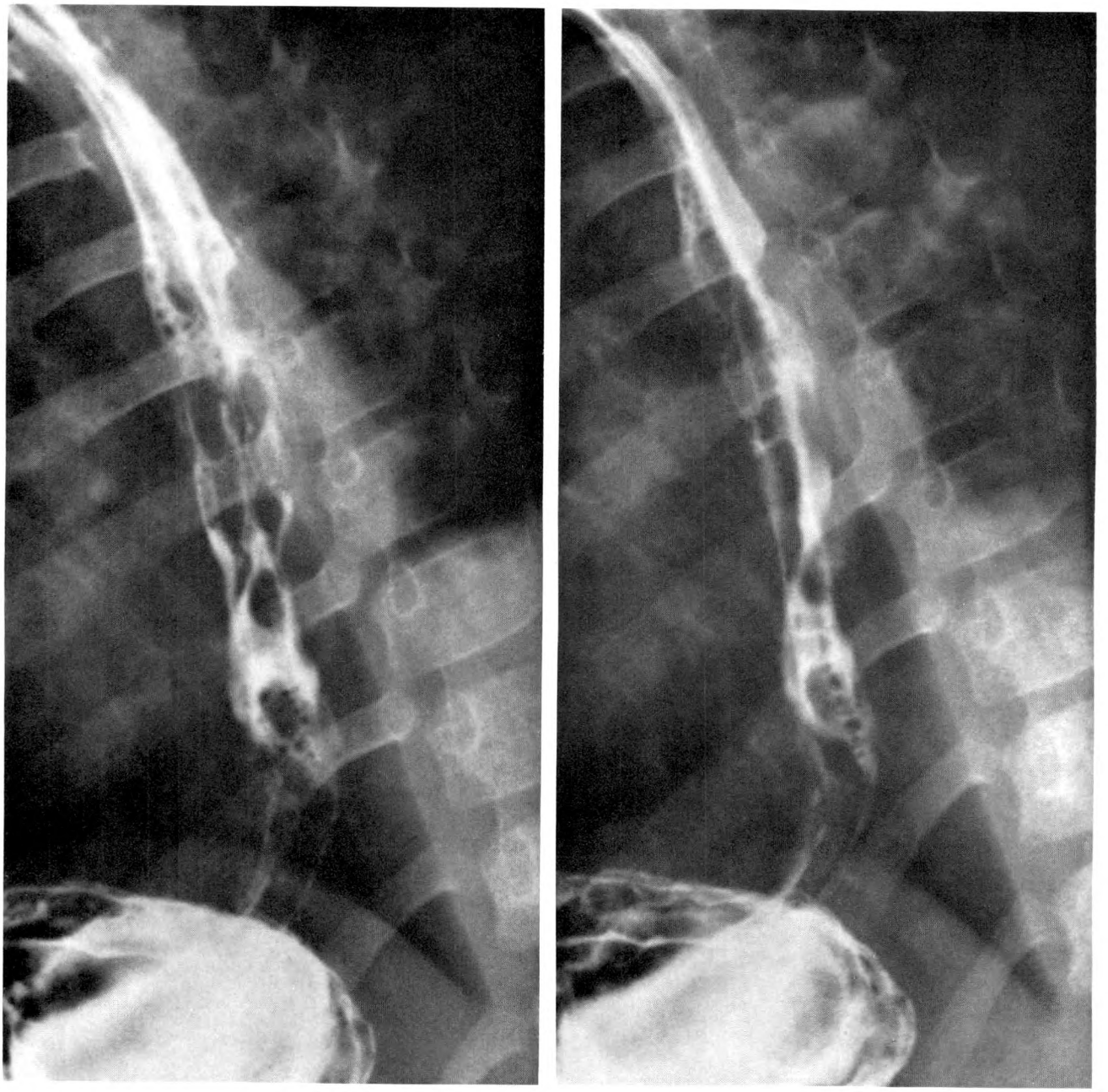
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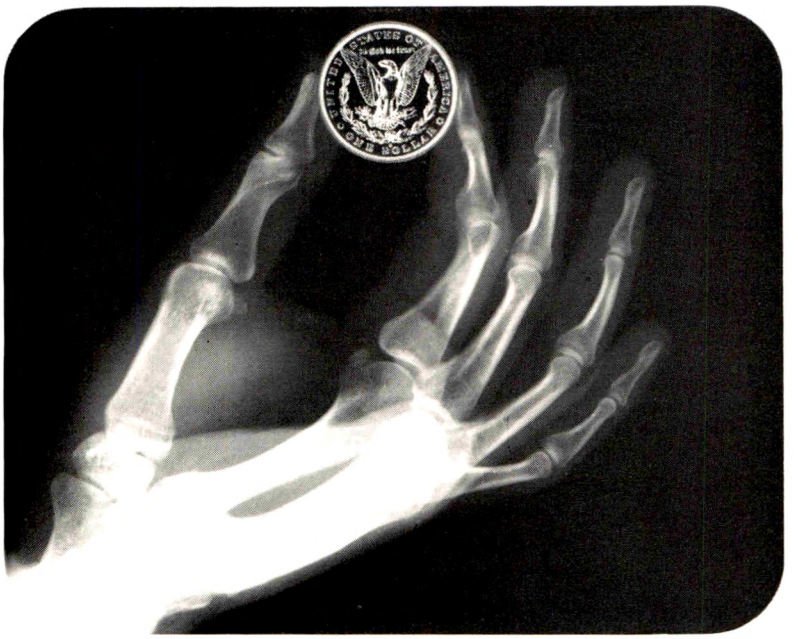
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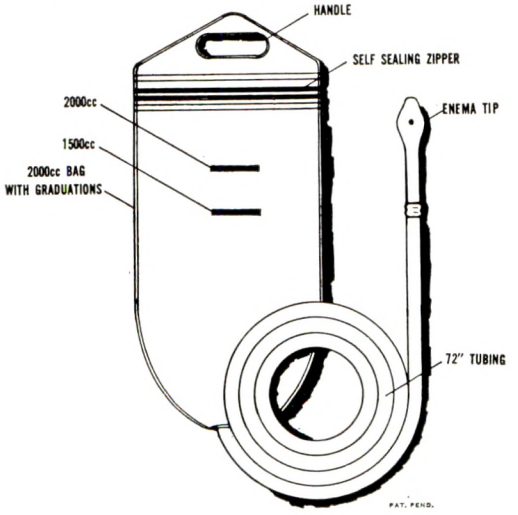
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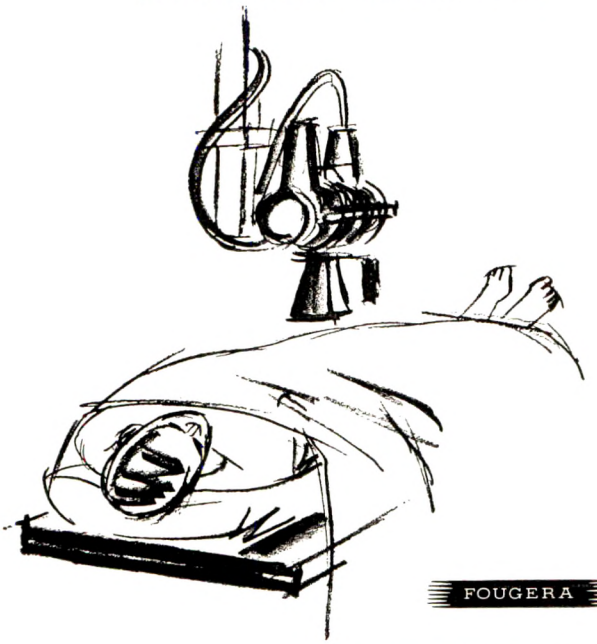
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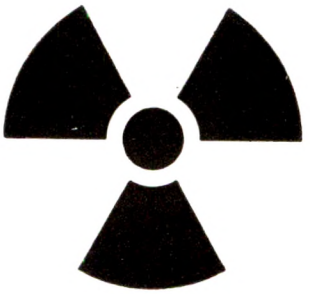
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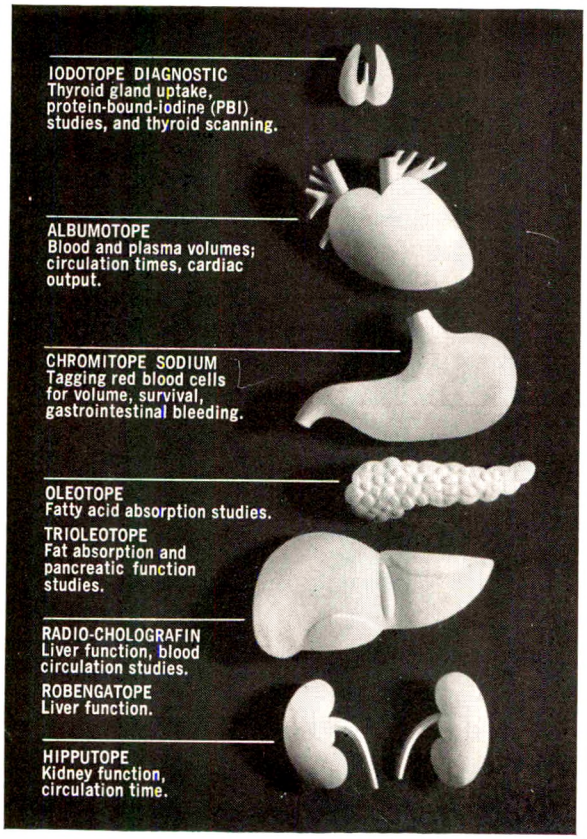
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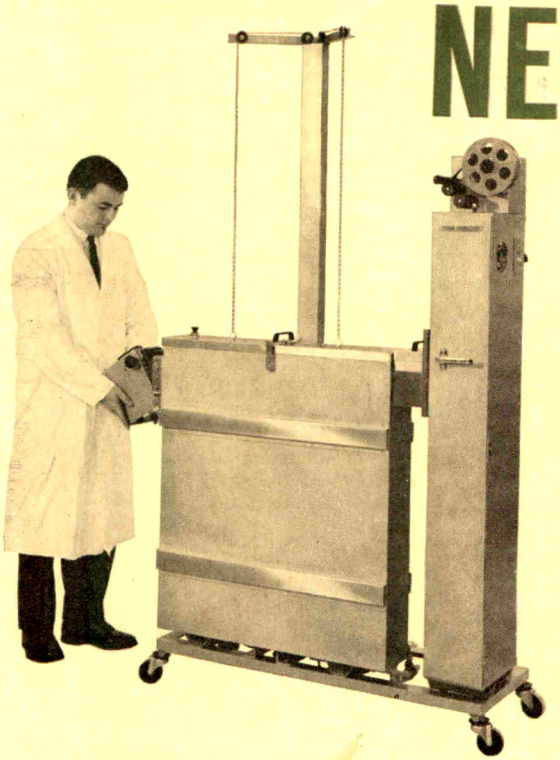
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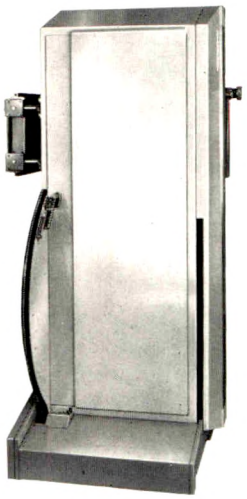
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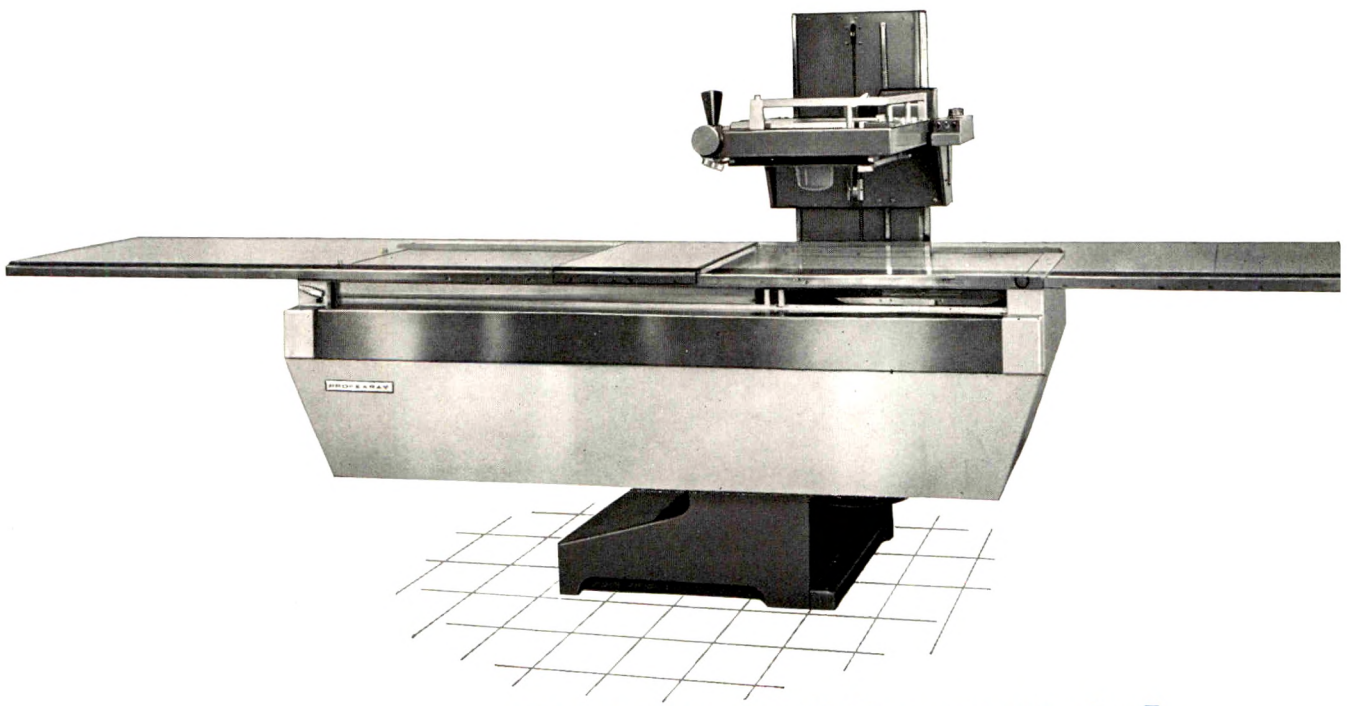


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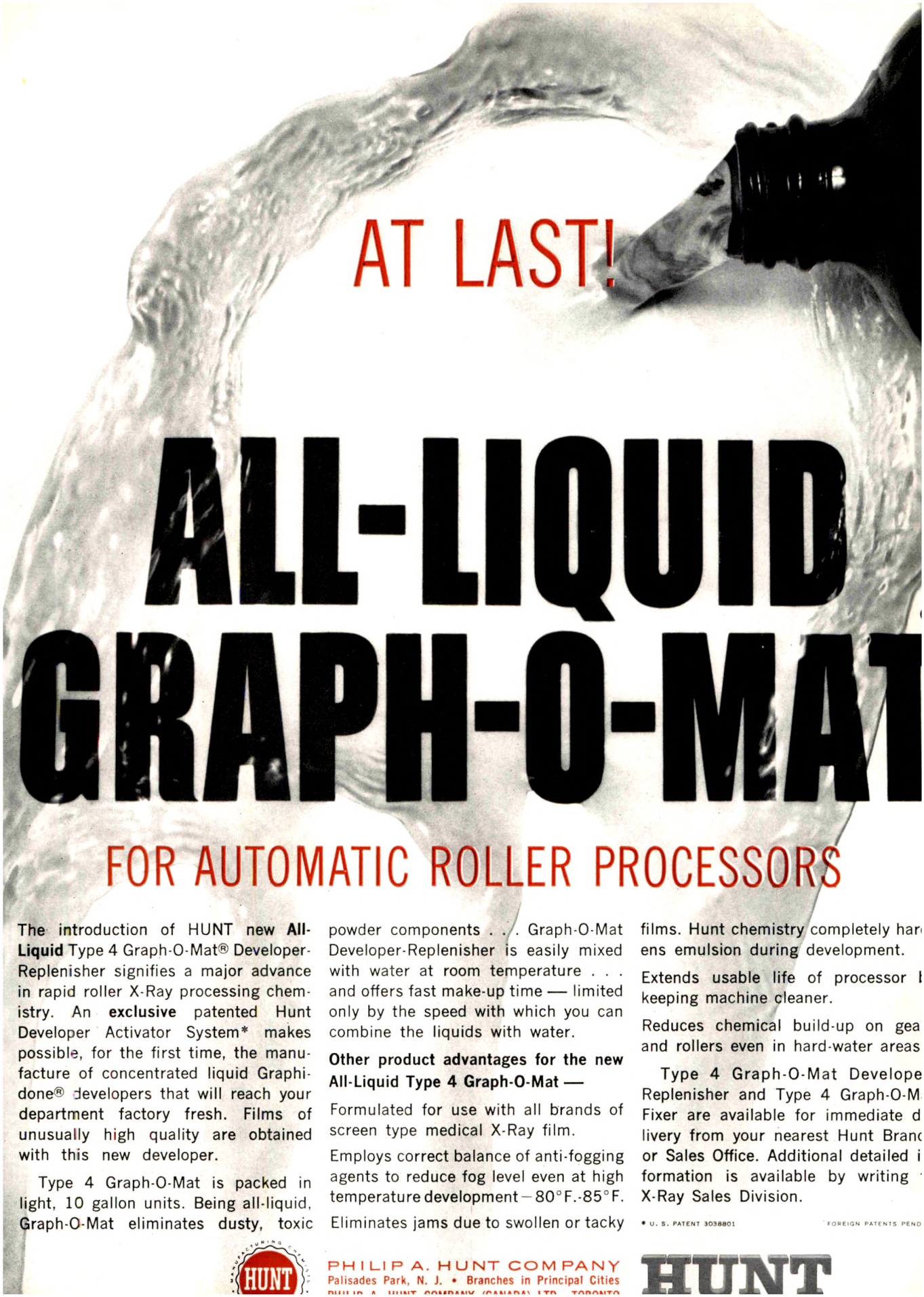
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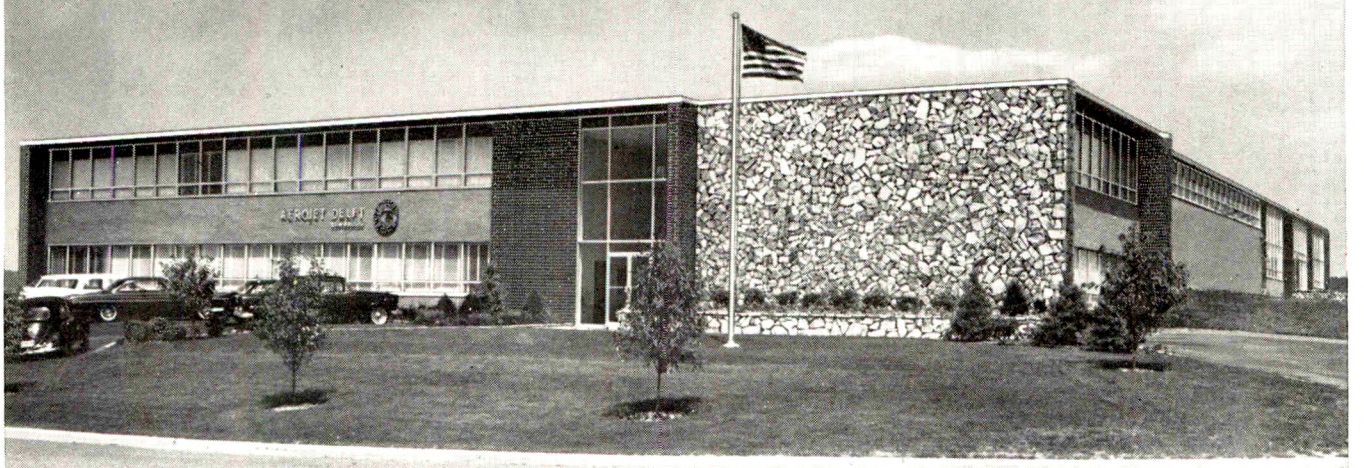
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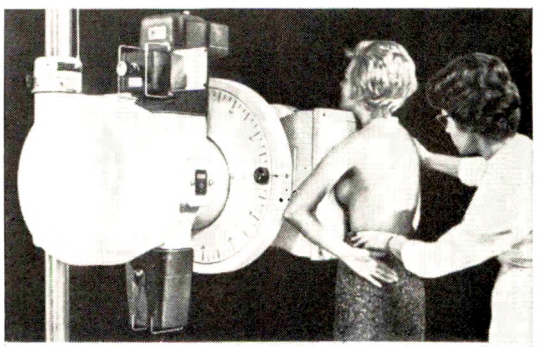
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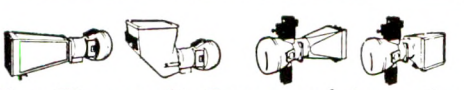


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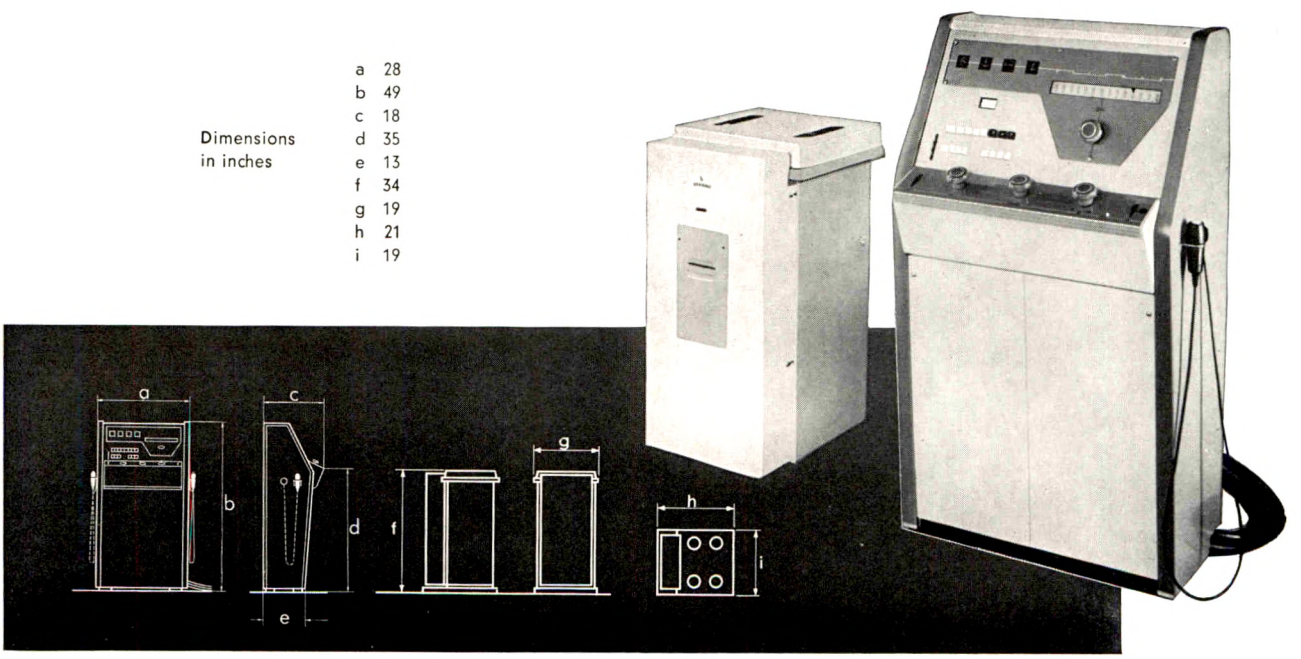
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THE AMERICAN JOURNAL OF ROENTGENOLOGY
RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 88 NOVEMBER, 1962 No. 5

A CRITICAL ANALYSIS OF CURRENT THERAPY OF CARCINOMA OF THE OVARY*

INTRODUCTION TO SYMPOSIUM

By PHILIP RUBIN, M.D.†
ROCHESTER, NEW YORK

ANY serious attempt to critically analyze the reports in the literature on the treatment of ovarian carcinoma is fraught with difficulty. Claims and counterclaims have appeared for virtually three decades regarding the value of surgery and radiation therapy. The flagrant lack of uniformity in reporting data is a major dilemma which has made cross-comparison of results impossible.

The survival figures following all modes of treatment in ovarian tumors are discouragingly low as compared to other gynecologic neoplasms. In carcinoma of the cervix and uterus, the improved methods of detection and diagnosis coupled with refinements in therapy techniques have led to better results. In the literature of ovarian cancer, a note of optimism is rarely sounded and is lost in the symphony of recorded pessimism. This has led to therapeutic policies of indifference and nihilism by some. On the other hand, the search for different approaches may lead to the indiscriminate use of newer measures without insight as to the limitations of the modality.

A review of 25 prominent reports appearing in the last two decades and dealing with the subject under discussion shows that conclusions often lack the support of statistical corroboration. In setting minimum criteria to evaluate certain specific points, a tabulation of vital information is given in Table I. The score to essential questions is a simple but striking critique of what has been published (Table II).

Regarding the Type and Adequacy of Treatment. In evaluating the efficacy of a type of treatment, it is necessary to know what was done. Although most articles mention the type of surgery preferred, all details apply to early cases where a hysterectomy is possible. Few mention what is recommended for situations in which neoplasms are inoperable although scored as adequate in the table. Mention of omentec-

* Presented at the Forty-third Annual Meeting of the American Radium Society, Colorado Springs, Colorado, May 11–13, 1961.
† Chief, Division of Radiation Therapy and Radioisotopes, University of Rochester Medical Center, Strong Memorial Hospital, Rochester, New York.

Table I

CRITIQUE OF LITERATURE ON OVARIAN CANCER TREATMENT

Yr.	Authors	Description of Therapy		Criteria for Selection	Presentation of 5 Year Survival				Comparative Evaluation of Therapy			Statistical Validity	Attitude Toward Irradiation	Absolute 5 Yr. Survival (per cent)
		Surgery	Irradiation		By Anatomic Stage	By Histologic Type	By Histologic Grade	By Dual Classification	Surgery	Surgery and Irradiation	Both By Dual Classification			
'60	Kent and McKay	+	+	o	+	+	+	+	+	+	o	+	+	36.4
'59	Murphy	+	+	R	+	+	o	o	+	+	+	−	+	24.4
'59	Turner, ReMine and Dockerty	+	±	o	+	+	+	o	+	+	o	−	±	49.4
'57	Latour and Davis	+	+	o	+	o	o	o	+	+	o	o	−	37.0
'57	Munnell, Jacox and Taylor	+	+	o	+	+	+	+	+	+	+	o	+	23.8
'57	Carlin and Frodey	+	o	o	+	o	o	o	+	+	o	+	+	23.3
'57	Chu	+	+	R	+	+	o	o	+	+	o	−	+	25.0
'57	Henderson and Bean	+	o	o	+	o	o	o	o	o	o	−	+	18.1
'56	Davis and Latour	+	+	o	+	o	+	o	+	+	o	o	−	37.6
'56	Hesseltine and Smith	o	o	o	o	+	o	o	o	o	o	−	−	18.8
'56	Holme	+	+	o	+	+	o	+	+	+	o	o	+	25.5
'55	Gardiner and Slate	+	+	o	+	o	o	o	+	+	o	+	+	32.3
'55	Randall, J. H.	+	+	R	+	+	o	o	o	+	o	−	+	27.8
'55	Ellis	+	+	o	+	+	o	o	+	+	o	−	+	27.0
'54	Pearse and Behrman	+	o	R	+	o	o	o	+	+	o	−	+	18.4
'51	Schmitz and Majewski	+	+	o	+	+	o	o	o	o	o	−	+	20.3
'51	Wheelock, Fennell and Meigs	+	o	o	o	+	o	o	o	o	o	−	+	28.4
'51	Kerr and Elkins	+	+	R-I	+	+	o	+	+	+	o	−	+	31.5
'49	Munnell and Taylor	+	o	R-I	+	+	+	+	+	+	+	−	±	30.8
'49	Allan and Hertig	+	o	R	o	+	o	o	+	+	o	+	+	35.0
'48	Freed and Pendergrass	+	+	R	+	o	o	o	o	+	o	−	+	39.2
'48	Montgomery	+	+	R	o	+	+	o	+	+	o	−	±	22.0
'46	Helsel	o	o	o	+	o	o	o	o	o	o	−	+	20.0
'41	Walter, Bachman and Harris	+	+	o	+	o	o	o	+	+	o	−	+	14.9
'40	Meigs	+	o	o	o	+	o	o	+	+	o	−	±	15.5
	Key:	+ = adequately detailed o = inadequately detailed		o = no criteria R = routine postoperative irradiation R-I = as above except Stage I	+ = data tabulated o = no data tabulated				+ = data presented o = no data presented			+ = statistically significant P = .05 − = not statistically significant o = data impossible to evaluate	+ = favorable ± = doubtful − = negative	

tomy is quite sporadic. Only 60 per cent of the articles give enough pertinent data to determine the radiation therapy factors used. By present standards the tumor dosage would be regarded as inadequate in the majority of references. Again the details are broad and vague and cannot apply to the entire experience in different stages of presentation.

Regarding the Basis of Case Selection. There is no truly randomized study by which to compare surgery versus surgery and postoperative irradiation in the literature. In approximately one-third of the series, all cases were treated postoperatively with irradiation with the occasional exception of Stage I patients by a few authors. The largest part of the literature indicates that the decision was based on the personal opinion of the staff members who in earlier stages would tend to select the more unfavorable cases by virtue of history and histology for irradiation. The reverse appears to be true of the more advanced cases where extremely debilitated patients seldom received irradiation.

Regarding the Reporting of Survival Figures. In at least 80 per cent of the reports survival is related to anatomic staging and in 64 per cent to histologic type. The importance of histologic grade has received increasing recognition as a prognosticator of response and survival in current reviews. Few attempts at offering a more informative type of dual classification incorporating histologic type and grade as well as anatomic stage are available.

Regarding the Comparative Evaluation of Therapy. Over-all survival figures related to surgery versus surgery and postoperative irradiation are available in 72 per cent of the reports. To rule out selection of cases, pathologic distribution patterns must be identified. Thus a comparable number of Stage II or III patients can be listed under two different therapy methods but weighting by virtue of the histology must be considered. The method of treatment, be it surgery alone or surgery and irradiation, may reflect the selection of cases rather than the superiority or inadequacy of the procedure.

TABLE II

CRITIQUE OF LITERATURE ON THERAPY OF OVARIAN CANCER

1. Is the description of therapy adequate to determine what was done?		
Surgery	23/25	92%
Irradiation	15/25	60%
2. Are the criteria for case selection presented?		
Unselected	0/0	0%
Majority irradiated	9/25	36%
No criteria offered	16/25	64%
3. How are survival figures presented?		
By anatomic stage	20/25	80%
By histologic type	16/25	64%
By histologic grade	6/25	24%
By dual classification	5/25	20%
4. Is the comparative evaluation of therapy tabulated?		
Surgery versus surgery and postoperative irradiation	18/25	72%
The above by dual classification	3/25	12%
5. How many series are statistically significant?		
Significant	4/25	16%
Not significant	17/25	68%
Inadequate data to evaluate	4/25	16%

Regarding Statistical Validity of Series. For the most part the articles reviewed gave little statistical evidence either for or against the use of irradiation in the treatment of ovarian cancer. In several cases the authors precipitously reported results as meaningful where the results were not significant statistically. By significant, we mean a difference at the 5 per cent level if our statistical model accurately represents the clinical situation; a difference as large as this would be expected only once in twenty independent trials.

Only four series met this test of significance and have a $P = .05$ or less. Most of these represent a broad comparison of patients treated with and without irradiation but lacking qualification as to stage and histology. Interestingly, all showed that the addition of irradiation yielded superior results.

The most important point to remember, however, is that in order to validly measure

the effectiveness of treatments there should be an element of random assignment of the treatments.[4,34] In any statistical analysis, it is *assumed* that there is such an element or else the data *act as if* there were such an element. In 100 per cent of all the available data published there is no way of knowing (outside of subjective assessment by a physician) how an individual was assigned to one treatment group or another. There is thus no way of deciding whether or not the data act like data from a randomized experiment.

The symposium has been organized to define and clarify the issues of controversy in regard to past treatment methods employed in ovarian cancer. In particular, the following problems will be considered:

What are the pathologic features of certain ovarian carcinomas?

Is surgery alone adequate?

Has postoperative irradiation proven itself?

Is preservation of the uterus worthwhile?

PRESENTATION OF DATA

As with other neoplasms, a classification of this cancer is necessary to allow for a framework from which to present data and to amplify the philosophy of management. In the majority of reports the anatomic staging of carcinoma of the ovary has been stressed as the most significant factor in prognosis and the results have been presented in a fashion similar to that in carcinoma of the cervix cases. Although a few authors have felt that the histology of the tumor is of little value in prognosis, recent reports have emphasized the importance of histologic typing and grading. One of the main inadequacies of past reporting can be overcome by employing a dual classification based on the *anatomic* extent of involvement and the *histologic* type and grade of the tumor.

ANATOMIC STAGING

The anatomic staging offered in the literature has never been purely clinical as in cases of cervical carcinoma. No author had advocated a staging of disease prior to surgery. This would seem to be rather academic. In virtually all instances the necessity to establish a diagnosis has led to laparotomy and surgical exploration with the exception of Stage IV neoplasms diagnosed via paracentesis. The central theme upon which staging has evolved is in regard to the operability and resectability of the carcinoma. The accuracy in surgical staging is essential to outlining a therapeutic plan. The need for a radiotherapeutic postsurgical anatomic staging has been suggested by Murphy.[42] The reason offered is that many radiotherapists receive patients with poor operative records. Although this has some merit, it rarely is necessary where cooperation between the gynecologist and radiotherapist is good. The difficulty in distinguishing tumor from postoperative induration is also fraught with considerable error.

Most of the recent investigators refer to or have altered the classifications of Walter *et al.*,[60] Helsel,[16] Heyman,[19] Munnell and Taylor,[40] and Latour and Davis.[31] Although differences exist, it is more common to find areas of agreement amongst these authors. The anatomic staging offered herein is a modification and a combination of these systems (Table III).

TABLE III

ANATOMIC CLASSIFICATION OF OVARIAN CANCERS

I.	Tumor limited to ovary grossly, completely removed surgically, no evidence of microinvasion
II.	Tumor showing break through capsule, excrescences, infiltrated adhesions, grossly removed surgically, evidence of microinvasion of capsule, lymphatics, and blood vessels
II S.	Ruptured capsule or cyst with spillage of fluid
III.	Tumor infiltrates other pelvic viscera as fallopian tubes, uterus, other ovary, bladder, rectum, sigmoid, pelvic peritoneum, grossly limited to pelvis, surgically not completely removed
IV.	Tumor has metastasized beyond pelvis

HISTOLOGIC CLASSIFICATION

The value of a histologic classification of ovarian neoplasms has resulted in a spectrum of recorded opinion. There are those on one side of the spectrum who feel that histologic typing is of no importance in prognosis or radioresponsiveness of the tumor. Approximately, one-third of the papers reviewed[6,14–17,20,45] did not present data in regard to influence of histologic type and the outcome of the patient. The grading of the carcinoma is even more frequently de-emphasized. There are those on the other end of the spectrum who feel that the ultimate prognosis and understanding in the handling of patients with ovarian cancer is by a thorough analysis of the histopathologic types. Meigs,[35] Allan and Hertig,[1] Wheelock *et al.*,[61] and Kottmeier[26] have rated this factor as more important than anatomic staging.

The majority of writers in the past decade have considered both histology and anatomic extent although a dual classification of data presentation has been infrequent.

From the point of view of the practitioner, the classification must follow clinical experience to be of value. Admittedly, classifications based on embryogenesis and histogenesis are detailed and inclusive. Many pathologists are fascinated by the variety of neoplasms from the morphologic and endocrinologic aspects. Comprehensive listings of all tumor types do not allow, however, for practical numbers in each category to compare methods of treatment. Since the majority of cases, 80 per cent or more, are cystic or solid adenocarcinomas, these types have figured most prominently in clinical reports and have accordingly been emphasized in the classification to be offered (Table IV).

One major issue of controversy is the distinction between the borderline and low grade carcinomas. Borderline carcinomas are only included when obviously clinically malignant in Stages III and IV. An attempt at utilizing DNA content of malignant cells by a cytophotometric determination in Feulgen-stained preparations seems promising in this regard.[3] Kottmeier[26] has championed the importance of stromal invasion in his grouping of tumors rather than the histologic features of malignancy as polymorphia, atypia or mitosis of cells as a key factor in determining survival. By contrast, in recent articles Munnell and Taylor,[40] Kent and McKay,[23] and Turner, ReMine and Dockerty[59] have shown the value of epithelial grading of cystadenocarcinomas in affecting prognosis. Kottmeier[28] has observed that there is a parallel between his histologic classification and the classification of Taylor, suggesting a relationship between stromal invasion and epithelial atypia. The histologic classification proposed is a composite, therefore, of type and grade.

Although the grouping together of serous and mucinous cystadenocarcinoma may be viewed as ill advised, it has recently been felt that this is more valid than separating them. Kottmeier[27] has been a chief advocate of this approach. Recent pathologic literature shows that the mucinous material in ovarian carcinoma is true mucin and the term "pseudomucin" is therefore not used. Numerous series indicate that mucinous carcinomas have a more favorable outcome than serous tumors. In this regard, it should be mentioned that mucinous epithelium is not as inclined to malignant transformation as serous epithelium; *i.e.*, 30 to 40 per cent of serous

TABLE IV

HISTOLOGIC CLASSIFICATION OF OVARIAN CANCERS

A.	Well differentiated cystadenocarcinoma, serous and/or mucinous*
B.	Poorly differentiated cystadenocarcinoma, serous and/or mucinous
C.	Solid adenocarcinoma
D.	Endometrial type of adenocarcinoma.
E.	Special tumors: Granulosa cell carcinoma, dysgerminoma, arrhenoblastoma, etc.

* Includes borderline carcinomas.

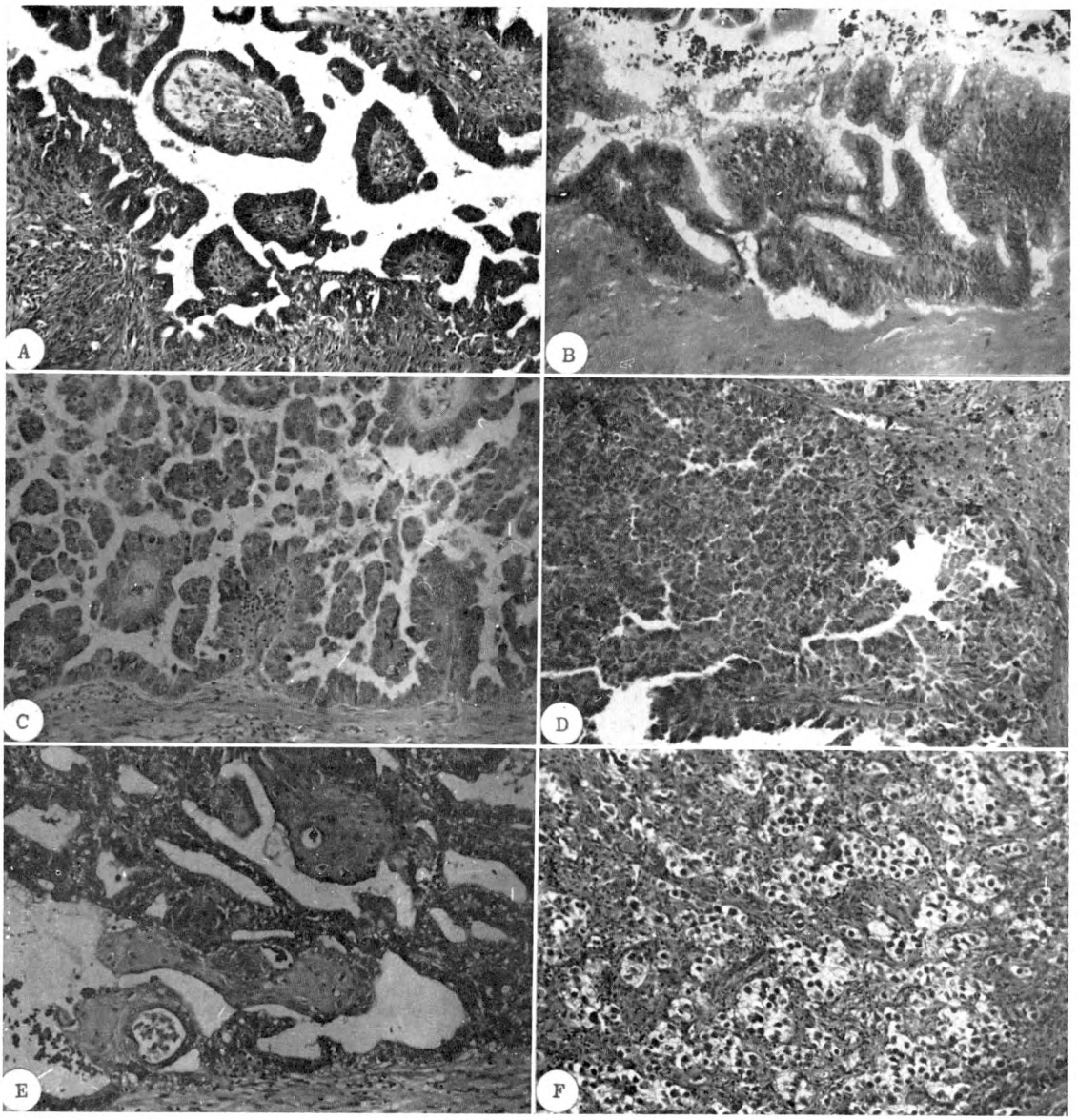


FIG. 1. Various types of ovarian carcinoma according to histologic classification. Magnifications are 120×. (*A*) Well differentiated serous cystadenocarcinoma, Grade 1, without evidence of stromal invasion. Type A. (*B*) Moderately differentiated mucinous cystadenocarcinoma, Grade 2, without stromal invasion. Type B. (*C*) Moderately differentiated serous cystadenocarcinoma, Grade 2, without stromal invasion. Type B. (*D*) Poorly differentiated solid adenocarcinoma with stromal invasion. Type C. (*E*) Adenoacanthomatous carcinoma probably arising in endometriosis. Type D. (*F*) Dysgerminoma showing typical clear cell appearance arranged in cords. Type E. (Courtesy Dr. Roger Terry.)

cystadenomas are carcinomatous as compared to 10 to 15 per cent of mucinous cysts. When each histologic type is graded, it is apparent that serous cystadenocarcinomas are much more frequently found to be less differentiated. For example, Kent and McKay[23] have shown that 54 per cent of mucinous lesions are Stage 1 carcinomas whereas only 27 per cent of serous and 23 per cent of solid tumors are in this stage. By the same token, only 7.1 per cent of mucinous carcinomas are Grade 3 in appearance mi-

Table V

OVARIAN CARCINOMA

University of Rochester Medical Center 1931–1955
Absolute 5 Year Survival According to Dual Classification

	A	B	C	D	E	Total
I	6/9	2/3	0/1	4/4	6/6	18/23 (78%)
II	4/5	4/6	0/4	5/5	3/4	16/24 (67%)
III	3/3	1/2	2/5	3/3	0/0	9/13 (69%)
IV	4/5	2/40	3/20	0/9	0/3	9/86 (10%)
Total	17/22 (77%)	9/15 (18%)	5/30 (16%)	12/21 (57%)	9/12 (43%)	52/145 (36%)

croscopically as compared to 31 per cent of serous tumors and 76 per cent for solid cancers. The prognosis appears to be similar for serous and mucinous carcinomas of similar grades. To emphasize the importance of grading, the serous and mucinous cancers are combined but separated by the degree of cellular differentiation.

Histologic Class A lesions are the well differentiated cystadenocarcinomas which include the borderline carcinomas (Taylor's borderline, Kottmeier's Class I) and well differentiated papillary carcinomas (Taylor's Grade 1, Kottmeier's Class II). In histolgic Class B are the poorly differentiated cystadenocarcinomas which include medium grade papillary cystadenocarcinomas (Taylor's Grade 2, Kottmeier's Class II–III) and high grade types (Taylor's Grade 3, Kottmeier's Class III). It is hoped that this simpler division will find wider acceptance amongst authors.

In conclusion, a table showing results following surgery and/or irradiation is presented to illustrate the desirable manner in which survival can best be analyzed (Table V).

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Note: The bibliography is appended to the article titled "Has postoperative irradiation proved itself?" by P. Rubin, M.D., Capt. J. W. Grise, USAF MC, and R. Terry, M.D. See pages 849–866.

ADDENDUM

The Cancer Committee[39] of the International Federation of Gynecologists and Obstetricians has attempted to standardize the classification of malignant ovarian neoplasms so that therapeutic reports throughout the world may be accurately compared. It has met at the Radiumhemmet, Stockholm, from August 24–26, 1961. The Conference considered in detail only the classification of neoplasms related to germinal epithelium since they include the vast majority of all ovarian cancers.

The Conference recommends that the common, epithelial tumors of the ovary be classified in the manner listed below.

Since good illustrations make definitions and descriptions of a tumor type more easily understood, the Conference decided to provide representative illustrations. The numbers in parenthesis in the classification which follows refer to figures published in "Tumors of the Ovary and Fallopian Tube" by Hertig, A. T., and Gore, H. (Atlas of Tumor Pathology, Section IX, Fascicle 33, Tumors of the Female Sex Organ, Part 3, Armed Forces Institute of Pathology, Washington, D. C., 1961).

1. *Serous cystomas*

(a) Serous papillary cystadenoma, benign (Fig. 69 and 71)

(b) Proliferating serous papillary cystadenoma without stromal invasion (possibly malignant) (Fig. 72 and 75)

(c) Serous cystadenocarcinoma, all grades (Fig. 78 and 81)

2. *Mucinous cystomas*

(a) Mucinous cystadenoma, benign (Fig. 87 and 90)

(b) Proliferating mucinous cystadenoma without stromal invasion (possibly malignant) (Fig 91 and 92)

(c) Mucinous cystadenocarcinoma, all grades (Fig. 93 and 95)

3. *Endometrioid tumors*

(a) .....*

(b) Proliferating endometrioid adenoma and cystadenoma (possibly malignant) (Fig. 102)

(c) Endometrioid adenocarcinoma, all grades (Fig. 77 and 105)

4. *Undifferentiated carcinoma* (cell type unknown)

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* The existence of a blank space after (3a) is due to the fact that there is as yet no agreement as to whether some cases of ovarian endometriosis may properly be classed as true tumors or all must be regarded as simply displaced or ectopic endometrium.

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PATHOLOGIC FEATURES OF CERTAIN OVARIAN CARCINOMAS*

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EIGHTY per cent of ovarian tumors are cystic, and most of these are benign. Twenty per cent are basically solid, and most of these are malignant. Ninety-six per cent of ovarian growths affecting women who are less than thirty years of age are benign, whereas 66 per cent of those found in women more than sixty years of age are malignant. Ten per cent of ovarian cancers are metastatic. These are often bilateral, but by no means always solid. Even experts may mistake metastatic for primary ovarian neoplasms.

Five per cent of ovarian cancers function physiologically and cause endocrine symptoms which may suggest the diagnosis. The remainder are asymptomatic in the early stages. All too often, therefore, the first manifestations are those of advanced disease, such as abdominal enlargement, which may be caused by peritoneal involvement with ascites or by carcinoma confined to the interior of an enlarging ovarian cyst.

Delay in diagnosis is the main reason for the gloomy prognosis in cancer of the ovary. Frequent pelvic examinations have been proposed to achieve early diagnosis, but improvement on this basis has not been obtained. Perhaps physicians have not yet learned the importance of investigating small masses in the pelvic adnexa.

Delayed treatment is another reason for the poor prognosis. Clinicians should consider malignant, until proved otherwise, every adnexal mass in a woman more than 35 years old. Doctors and patients share responsibility for delayed treatment.

The third reason for the poor prognosis concerns failure to recognize cancer at laparotomy. Reports on sizable series of patients with ovarian cancer rarely indicate that more than 30 per cent of patients undergoing laparotomy had a cancer operation. The diagnosis of malignancy too often comes as a surprise and the surgeon is reluctant to go back and clean out the pelvis. The series of cases reported in this paper differ from others in that all patients were well enough to travel, but another difference is that, in these patients, cancer was diagnosed microscopically, typed, and graded within minutes of the time the surgeon opened the abdomen. In a number of instances examination of fresh frozen sections saved the patient a good deal more than the inconvenience of a second laparotomy.

Criteria for determining prognosis after the diagnosis has been made include the anatomic stage, the microscopic grade, and the type of cancer.

MATERIALS AND METHODS

This study includes 172 consecutive patients with ovarian cancer seen at the Mayo Clinic over a 5 year period.[1] Since there were 5 operative deaths and 3 patients were lost to follow-up, survival percentages relate to only 164. All patients seen were included except (1) those with metastasis, (2) those with functioning tumors, and (3) those whose cancers had been first treated elsewhere. We did include 26 patients who had been operated on elsewhere for nonmalignant pelvic conditions, the operation consisting of hysterectomy with preservation of the ovaries in 14.

Primary treatment for the 172 patients was surgical, and a specimen for frozen section study was taken in each instance. Ninety-five patients had postoperative irradiation.

* Presented at the Forty-third Annual Meeting of the American Radium Society, Colorado Springs, Colorado, May 11–13, 1961. Part of the Symposium: A critical analysis of current therapy of carcinoma of the ovary.

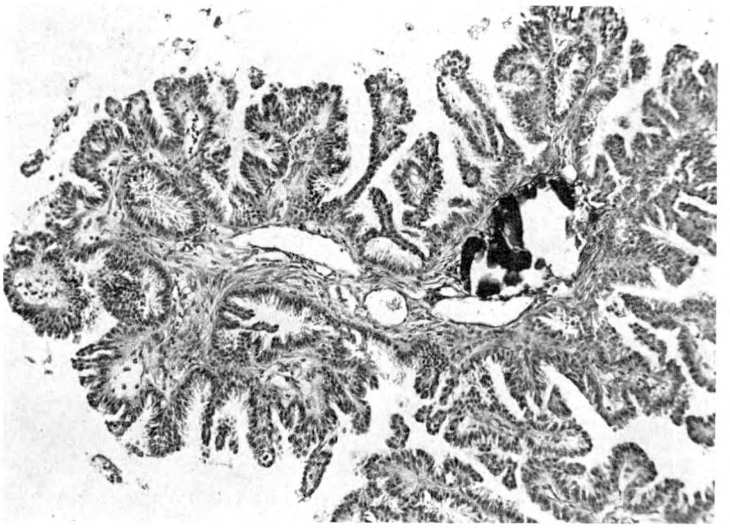


FIG. 1. Papillary adenocarcinoma, Grade 1 (Type A) with psammoma bodies. Many pathologists erroneously classify this as a borderline lesion. Axillary metastasis developed in the patient from whom this specimen was taken 42 years following removal of the bilateral primary ovarian growths (hematoxylin and eosin; ×100).

Gross Typing. Our method of expressing the extent of ovarian cancer was as follows: In Stage I, cancer is confined to one ovary. Solid as well as cystic lesions are included. In Stage II, superficial excrescences are present or a malignant cyst has been ruptured. All gross cancer is removable, but microscopic seeding is probably present. Bilateral ovarian involvement has been placed in this category; however, it is believed that bilateral encapsulated ovarian cancers belong in Stage I. In Stage III pelvic peritoneal implantation is obvious, or the tumor is adherent to structures in the pelvis. In Stage IV omental caking and other evidence of extrapelvic spread are present.

Grading. Grading is a microscopic proposition and in the Broders method, which is employed at the clinic, it is conducted without reference to the gross extent of the lesions or to the specified type of cancer. The four grades are illustrated in Figures 1 through 4.

Tumor "Species." In addition to gross typing and microscopic grading, attention must be directed toward the identification of various species in the ovarian tumor family. This is so because differences in behavior of the various species influence the prognosis. Eight species which fit into the classification proposed by others are as follows: (1) serous cystadenocarcinomas are characterized by three features—a basically cystic nature, the presence of internal or external papillary fronds, and a usually low microscopic grade; (2) mucinous cystadenocarcinomas are predominantly cystic and usually bilateral, and they generally have a low microscopic grade. Intracystic papillary fronding may be present. (These first two species correspond with lesions sometimes categorized as Type A); (3) seroanaplastic adenocarcinomas are frequently bilateral and are predominantly solid. This tumor has been regarded by some as a highly malignant variant of serous cystadenocarcinoma; however, origin from cystadenoma can rarely be traced. Accounting for more than 20 per cent of primary ovarian cancers, this species is responsible for many of the extensive inoperable ovarian growths. (My category of seroanaplastic carcinoma combines Types B and C, categories sometimes used by others); (4) endometrial-like adenocarcinomas (Type D), including about 10 per cent of ovarian tumors, comprise malignant endometriomas, adenoacanthomas, and other nonpap-

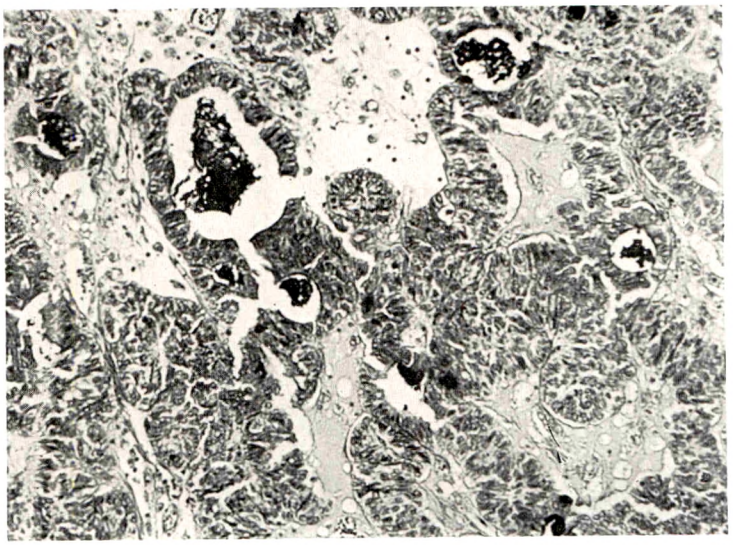


Fig. 2. Papillary adenocarcinoma, Grade 2 (Type A) mucous type. There is reasonably good glandular formation, and the cells for the most part are moderately well differentiated (hematoxylin and eosin; ×80).

illary growths with strong microscopic resemblances to cancer of the endometrium. Indeed, in many instances there is simultaneous involvement of the endometrium by a similar type of tumor. The grade of malignancy is ordinarily low; (5) special tumors (Type E) include malignant teratomas, mesonephromas, hypernephroid tumors, and mixed serous and mucinous adenocarcinomas which account for small numbers of ovarian tumors.

RESULTS

The 5 year survival rates of the traced patients according to the stage of the lesions were 92.1 per cent (35) of the 38 traced patients with Stage I, 88.2 per cent (30) of the 34 traced patients with Stage II,

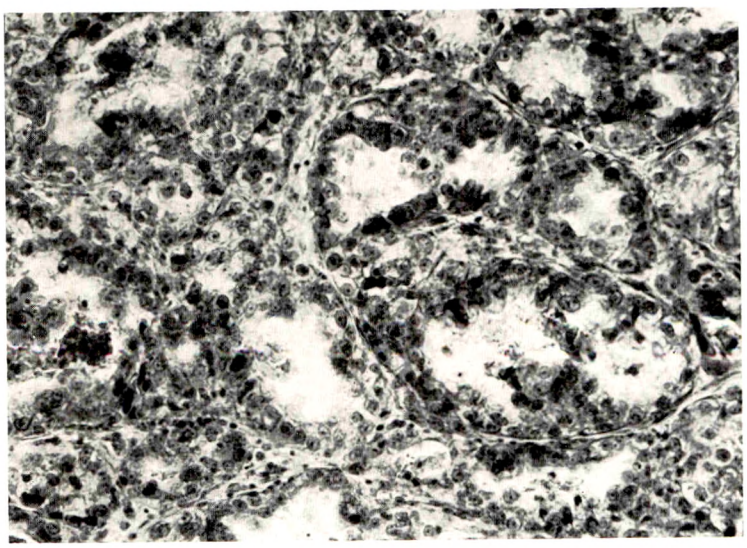


Fig. 3. Adenocarcinoma, Grade 3 (Type C). Formation of glandular spaces is still discernible, but the constituent cells exhibit some macronucleoli and other features of anaplasia (hematoxylin and eosin; ×170).

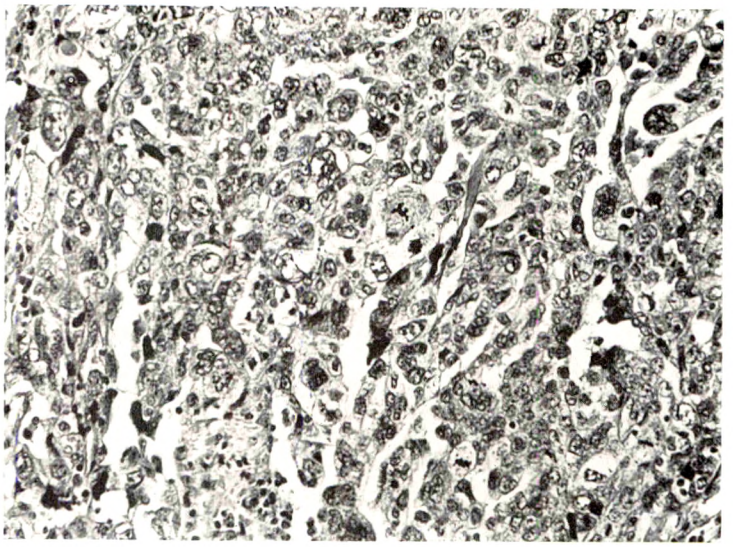


FIG. 4. Solid adenocarcinoma, Grade 4 (Type C). Cell cording rather than glandular formation characterizes this growth. Variations in size of cells and staining are apparent. A pathologic mitotic figure is just below and to the left of center (hematoxylin and eosin; ×170).

44.0 per cent (22) of the 50 patients with Stage III, and 4.8 per cent (2) of the 42 patients with Stage IV lesions. While the need for earlier diagnosis is strongly reflected, justification of a radical approach in Stage III lesions is evident. The salvage of almost 5 per cent of patients with irremovable growths must be attributable to a favorable response to irradiation.

According to grade of malignancy, the 5 year survival rates of the traced patients were 82.8 per cent (53) of 64 patients with Grade 1, 57.9 per cent (22) of 38 with Grade 2, and 22.6 per cent (14) of 62 with Grade 3 and 4 lesions. In Grade 3 or 4 tumors there was good clinical correlation with rapid growth and extension. Mucous and endometrial types tended to display low-grade lesions, while a high proportion of teratocarcinomas and anaplastic adenocarcinomas were of Grades 3 and 4.

Table 1 shows survival data on the patients according to the tumor species or pathologic type. Serous cystadenocarcinomas at times gave evidence of origin from their benign counterpart. Psammoma bodies were helpfully present in half of the cases. The incidence of this type was 45 per cent. In 10 per cent of our patients with mucinous cystadenocarcinoma, rupture of the tumor with spillage occurred, producing jelly-belly. The incidence of this type of tumor was 12 per cent. The lesions were almost universally of low grade, microscopically.

Five year survival rates of traced patients according to the method of treatment were 64.8 per cent (46) of 71 receiving surgical treatment only and 46.2 per cent (43) of 93 receiving irradiation postoperatively.

SUMMARY

To indicate that survival of patients with primary carcinoma of the ovary may be improved by early diagnosis, early and adequate treatment, and frozen section biopsy during the initial operation, the records of 172 consecutive patients without metastasis, functioning tumors, or a history of prior cancer treatment were reviewed. In each instance radical operation was made possible by examination of fresh frozen sections. More than half of the patients received supplementary irradiation. An operative mortality rate of less than 3 per cent and a 5 year survival rate of 54.3 per cent were achieved.

Table I

FIVE-YEAR SURVIVAL RATES BY PATHOLOGIC TYPE

Lesion	No. of Patients		Lived 5 Years or More after Operation*	
	Total	Traced	No.	Per cent
Cystadenocarcinoma				
Papillary serous type	75	73	45	61.6
Mucous type	21	20	13	65.0
Mixed serous and mucinous type	4	4	4	†
Adenocarcinoma				
Seroanaplastic type	34	34	6	17.6
Endometrial type	19	19	13	68.4
Mesonephroma type	8	8	4	†
Teratoma associated with carcinoma	3	3	1	†
Hypernephroid type	3	3	3	†
Total	167	164	89	54.3

* Based on traced patients. Inquiry as of January 1, 1956. Hospital deaths excluded in calculation of survival rates.
† Group too small to be statistically significant.

Since survival also varies with the gross stage of tumor development, the microscopic grade of the tumor, and the tumor species or type, consideration was given to each of these factors. Ninety-two per cent of 38 patients with Stage I tumors but only 5 per cent of 42 with Stage IV tumors survived 5 years. Eighty-three per cent of 64 patients with Grade 1 tumors but only 23 per cent of 62 patients with Grade 3 or 4 tumors survived 5 years. More than 60 per cent of 112 traced patients with cystadenocarcinoma or endometrial type of carcinoma and less than 18 per cent of 34 traced patients with seroanaplastic adenocarcinoma survived 5 years.

The Mayo Clinic
Rochester, Minnesota

REFERENCE

1. Turner, J. C., Jr., ReMine, W. H., and Dockerty, M. B. Clinicopathologic study of 172 patients with primary carcinoma of ovary. *Surg., Gynec. & Obst.*, 1959, *109*, 198–206.

IS SURGERY ALONE ADEQUATE?*

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THE Department of Obstetrics and Gynecology of the University of Colorado has depended on surgery as the main form of treatment for ovarian malignancies, but postoperative radiation therapy has been an important adjunct. However, in reviewing our survival results, it is believed that irradiation, including deep roentgen-ray and/or radioactive gold therapy, has only slightly improved the end results. Surgery consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy, sometimes with omentectomy. If the patient is inoperable, the lesion is biopsied, the abdomen closed, irradiated, and then reoperation is performed later if feasible.

MATERIAL

We have reviewed our experience with 122 patients with ovarian malignancies seen between July 1, 1946, and December 31, 1960. This is our entire group of malignancies of the ovary. Table 1 shows the anatomic and histologic grouping of all cases and the survival rates for each group. Some were treated 15 years ago, some only 12 months ago. Some were so far advanced on admission that no treatment whatsoever was administered. It is important, however, we think, to include all patients presenting to an institution with a particular disease in evaluating the end results and not just those chosen for therapy.

Of the 122 patients with ovarian malignancies, 44 of the group or 36 per cent are alive and well without evidence of recurrent or existent disease at this time. It is estimated that 7 of the 44 surviving patients will have recurrent disease within the next 4 years. These patients have been recently diagnosed as Stage IV cases. This will reduce our cure rate from 36 to 30 per cent.

Over one-half or 23 of the living 44 patients are in the Stage I anatomic class; A, B, and E histologic types. It is conceivable that none of these 23 patients needed postoperative irradiation although 9 of the 23 received it. The results represent 100 per cent survival in Stage I cases. Thirteen of 18 (72 per cent) in Stage II cases are alive and well; 9 of the 13 had postoperative irradiation. Perhaps some would have lived

TABLE I

TOTAL NUMBER OF CASES AND SURVIVORS IN EACH GROUP OF OVARIAN CARCINOMAS

Anatomic Stage	Histologic Type										Total No. of Cases	Total No. of Survivors
	A		B		C		D		E			
	Total	Survivors	Total	Survivors	Total	Survivors	Total	Survivors	Total	Survivors		
I	11	11	2	2	0	0	0	0	10	10	23	23
II	3	2	9	6	1	1	0	0	5	4	18	13
III	1	0	1	0	2	0	0	0	0	0	4	0
IV	17	2	39	6	15	0	0	0	6	0	77	8
Totals	32	15	51	14	18	1	0	0	21	14	122	44

* Presented at the Forty-third Annual Meeting of the American Radium Society, Colorado Springs, Colorado, May 11–13, 1961. Part of the Symposium: A critical analysis of current therapy of carcinoma of the ovary.

without benefit of irradiation since the surgeons felt that all of the tumor had been excised by primary surgery. The one patient with solid adenocarcinoma listed under Stage II C, however, is probably alive because of deep roentgen-ray therapy. This patient had to be reoperated on because of recurrent ovarian cancer. The second operation was followed by radiation therapy and now, 7 years post therapy, she is without evidence of recurrence. There are no survivors among our 4 patients in the Stage III group. Irradiation was of no benefit in these cases. Eight of 77 patients in Stage IV are presently alive and well, but in 7 of the 8 cases 5 years have not elapsed since treatment. There are only 2 patients in the entire series of 122 in whom there is evidence that postoperative radiation therapy is the reason for survival. There may be several others in whom irradiation was a deciding factor, but this is not possible to determine.

DISCUSSION

Before it can be stated whether surgery alone is adequate, one must define what adequate surgery is. In general, total abdominal hysterectomy, extra-fascial type, with bilateral salpingo-oophorectomy is the type of surgical procedure that should be used for the treatment of ovarian cancer. There are a few exceptions in Stage I, Type E cases that should be mentioned. The young patient with a granulosa cell tumor, thecoma, luteoma, or dysgerminoma need not have a total hysterectomy and bilateral salpingo-oophorectomy as part of treatment if the tumor is confined to an ovary and has not broken through the tumor capsule. In such a patient removal of the tube and ovary on the diseased side is adequate surgical treatment. All other patients with Stage I carcinoma of the ovary should have a total abdominal hysterectomy and bilateral salpingo-oophorectomy, as should all patients with Stage II and III disease. Omentectomy has a debatable value and has not been used consistently in our series as part of the primary surgical treatment of ovarian cancer.

TABLE II

PERCENTAGE SURVIVAL OF PATIENTS IN EACH GROUP

Anatomic Stage			
I	II	III	IV
100%	72%	0	10%

Histologic Type				
A	B	C	D	E
47%	27%	6%	No Cases	67%

Total 36%

The surgery performed for Stage IV patients is a matter of judgement. Some Stage IV patients are inoperable; other Stage IV patients can only be identified as Stage IV cases after the abdomen has been entered. Under these circumstances it may be best to biopsy the lesion and then close the abdomen. Such a patient should probably be referred for external radiation therapy or chemotherapy. If either form of treatment is beneficial, a later operation may be contemplated to remove as much of the primary lesion as possible, as well as the uterus, cervix, and the other tube and ovary. Many Stage IV patients are beyond the help of surgery or radiation therapy when first seen.

The reason that the uterus, tubes, and ovaries must be removed in the management of Stage I, Type A, B, C, and D, and Stage II and III cases is that metastases to the opposite ovary occur in 15 to 25 per cent of these ovarian cancers. The endometrium and tubes are involved in 8 to 15 per cent of all Stage I, II, and III cases, excepting Stage I, E. There is no place for subtotal hysterectomy in the surgical treatment and there is no advantage in leaving the uterus behind for possible radium application later.

Prophylactic oophorectomy is not performed in our institution. The ovaries serve a valuable function even after menstruation halts normally and ovarian cancer is a very rare disease. If the ovaries are normal, they are not removed unless the patient has

ovarian cancer on the opposite side (other than Stage I, E) or unless metastatic breast cancer is being treated.

When operable clinical recurrence is suspected, a second operation is carried out in selected patients. This has been beneficial in isolated cases.

CONCLUSIONS

1. Surgery consisting of total abdominal hysterectomy and bilateral salpingo-oophorectomy is the primary treatment of choice for patients with Stage I disease.

2. If the tumor has spread beyond the inner capsule of one ovary, *i.e.*, Stage II, III, or IV, postoperative radiation therapy, preferably with deep roentgen-rays, should be administered. It is difficult to determine whether this markedly improves survival rates; however, favorable results with several isolated patients who had advanced ovarian lesions and received irradiation indicate that deep roentgen therapy following primary surgery should be used for patients who are in Stage II, III, and IV.

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HAS POSTOPERATIVE IRRADIATION PROVED ITSELF?*

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CARCINOMA of the ovary is a complex disease process. It is a malignant growth of insidious onset, late diagnosis and grave prognosis. Most patients die of their disease despite the rapid advances in surgical and radiotherapeutic techniques. It is little wonder that the value of any procedure remains in doubt. Despite the cataloguing of thousands of cases in the literature, the capability of postoperative irradiation to ablate and cure residual ovarian carcinoma is an unsettled issue.

Although most authors have a favorable attitude toward radiotherapy as a useful adjuvant to surgery, the divergent point of view has its proponents. Meigs,[35] Montgomery,[36] and Munnell and Taylor[40] in their earlier report, all felt that irradiation was of some palliative value but rarely was it curative in ovarian carcinomas. Recently, Davis, Latour and Philpott[10] in a series of articles have sharply questioned the use of postoperative radiotherapy. In their critical evaluation of other authors, they note that impressions are given as much credence as facts since statistical corroboration is lacking. They claim that their experience as well as that of others has failed to show a statistical difference between those patients treated by surgery alone versus surgery and irradiation and that, since radiation therapy is not a benign procedure and has failed to prove itself, its use should be sharply curtailed.

In response to a questionnaire sent to major university and cancer centers on this aspect of the subject, the majority of radiotherapists who answered advocate the use of irradiation but most expressed doubtful to frankly negative opinions in regard to its curative value. In attempting to assess the basis of this general attitude, the experience at Strong Memorial Hospital is presented since it is representative of much of the published and unpublished data on this subject. An attempt will be made to define the value of radiotherapy and dispel some of the prevalent skepticism, much of which is justified.

PRESENT SERIES

From 1931 to 1955, a total of 145 patients were histologically diagnosed and treated at Strong Memorial Hospital. All of the original pathologic diagnoses were reviewed and re-indexed according to the classification previously outlined. Most of the patients were followed in private offices or clinics and were counted as dead if lost to follow-up within the first 5 years after treatment. If survival beyond 5 years was established, the last year of survival has been tabulated with or without recurrence of disease.

A. TREATMENT METHODS

Surgery. As in any general hospital, a variety of procedures was employed which were dictated by circumstances. Although radical hysterectomy and bilateral salpingo-oophorectomy were performed in the earlier Stage I and II cases, resections on many occasions consisted of excision of the tumor and the involved ovary. Ten of the

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15 survivors in the surgery group had the more radical removal of female organs. In Stage III cases as much of the disseminated carcinoma as possible was removed surgically. Usually, a biopsy with removal of the larger masses was attempted in Stage IV cases—the group with abdominal metastases.

Radiation Therapy. As one might expect, there was a gradual evolution of radiation techniques in this time span. From 1931 to 1951, orthovoltage factors: 220 to 280 kv., half value layer of 1.0 mm. Cu, 10×15 cm. ports, and 30 degree angulated right and left, anterior and posterior pelvic fields were generally used. Occasionally, lateral pelvic fields were added. Depth doses ranged from 2,000 to 3,500 r with increased doses of 4,500 r being delivered at the end of this time period. From 1952 to 1955, 1 mev. irradiation utilizing a 15×15 cm. pelvic port was employed through a rotation of 360 degrees. Depth doses reached 5,000 r in 5 to 6 weeks. For abdominal irradiation the focal skin distance was increased to allow for better depth doses. Radioactive isotopes, particularly Au^{198}, evoked much enthusiasm in the early 1950's and a few patients were treated with radioisotopes only.

It would be unfair to assess the adequacy of therapy by present day capability and thereby eliminate cases having completed projected courses of irradiation. Although a large number of Stage IV patients received inadequate courses of therapy, it was decided to include all patients subjected to irradiation to avoid problems arising from case selection in reporting our survival figures.

B. CRITERIA OF CASE SELECTION

Most patients were routinely referred for postoperative irradiation except early Stage I cases. When the surgeon suspected that he had left residual disease, microscopic or gross, the patient generally received some form of irradiation. No attempt at randomization was made in prospect and none can be discerned in retrospect.

C. PRESENTATION OF SURVIVAL FIGURES

The major dilemma of ovarian carcinoma can be appreciated by the fact that 60 per cent of the series had abdominal metastases on presentation. Survival in the earlier stages was quite good and comparable to that in cases of carcinoma of the cervix (Table I). In Stage I, 78 per cent of the patients survived 5 years and in Stage II 67 per cent. The difference between the surgical and irradiated groups is not large enough to be significant. The 69 per cent 5 year survival for Stage III cases is surprising and will be elaborated upon later. The poor results in Stage IV patients (10 per cent) are expected and dictate the poor general survival at 5 years of 36 per cent for the whole series. The bearing that the stage of disease at the time of presentation has on survival rate is readily apparent.

The common presentation of histology by the types shown in Table II is less informative. Serous and mucinous carcinoma cases yield a similar survival pattern whereas the survival rate of solid carcinoma patients is much poorer. The best survival at 5 years was obtained in special tumor cases since the majority of these were granulosa cell carcinomas,[13] but also included are some mesonephromas[5] and a dysgerminoma.[1] All the 5 year survivors were granulosa cell carcinoma cases.

Of much more value is the re-classification by histologic type and grade (Table III). This was done by one of us (R. T.) without any knowledge of the status or survival period of the patients. Well differentiated cystadenocarcinomas have a fourfold better prognosis than a poorly differentiated cystadenocarcinoma, independent of type. This is the identical ratio that Kottmeier[26] noted in his experience between low grade Class II carcinomas and high grade Class III cancers, *i.e.*, 79.2 per cent versus 24.2 per cent 5 year survival. This is completely lost in the conventional serous and mucinous breakdown. Of particular interest is the identification of the "endometrial type" of adenocarcinoma, 28 per cent of which are adenoacanthomas; 23 per

Table I

OVARIAN CARCINOMA BY ANATOMIC STAGE
UNIVERSITY OF ROCHESTER MEDICAL CENTER 1931–1955
ABSOLUTE 5 YEAR SURVIVAL

	Surgery Alone	Surgery and Irradiation	Total
Stage I	10/11 (91%)	8/12 (62%)	18/23 (78%)
Stage II	4/7 (57%)	12/17 (70%)	16/24 (67%)
Stage III	0/0 (0%)	9/13 (69%)	9/13 (69%)
Stage IV	1/33 (3%)	8/52 (15%)	9/86 (10%)
Total	15/51 (29%)	37/95 (39%)	52/145 (36%)

cent of these tumors arise in endometriosis or endometriomas; and the remainder, the solid adenocarcinomas, arise both in ovary and endometrium so that the primary site could not be established. These were originally included with cystic and solid adenocarcinomas. The fact that the 5 year survival is 57 per cent confirms the impression of others[11,26] that this type of ovarian cancer has a more favorable prognosis and should be separated as a distinct group. The 5 year survival of these various subtypes was best in adenoacanthomas (4/7), followed by those arising in endometriosis (3/6) and then in the solid endometrial type of adenocarcinoma (5/11).

D. COMPARATIVE EVALUATION OF THERAPY

In comparing the results of surgery and surgery and postoperative irradiation, it is assumed that the cases were randomly selected. To ascertain if irradiation has contributed to survival, most authors regard the surgically treated cases of the series as a control group. As is true of many reports including the present one, this is rarely valid since differences in selection exist and can be best appreciated if a dual classification system, including anatomic stage and histologic type and grade, is used.

Table II

OVARIAN CARCINOMA BY HISTOLOGIC TYPE
UNIVERSITY OF ROCHESTER MEDICAL CENTER
1931–1955

Type of Tumor	Absolute 5 Year Survival
Serous	30/75 (40%)
Mucinous	6/16 (37%)
Solid	7/33 (18%)
Special tumors	9/21 (50%)
	52/145 (36%)

Stage I. (Table IV). There is some difference in the distribution of histologic cases but this does not account for the difference in survival in the surgically treated and irradiated groups. Reviewing the causes of death, it is noted that only 1 patient died with and because of her ovarian cancer. Three of the 4 patients in the irradiated

Table III

OVARIAN CARCINOMA BY HISTOLOGIC TYPE AND GRADE
UNIVERSITY OF ROCHESTER MEDICAL CENTER 1931–1955

Classification	Surgery	Surgery and Irradiation	Total
A. Well differentiated cystadenocarcinoma	6/7	11/15	17/22 (77%)
B. Poorly differentiated cystadenocarcinoma	1/14	8/37	9/51 (18%)
C. Solid adenocarcinoma	1/13	4/17	5/30 (16%)
D. Endometrial type of adenocarcinoma	3/5	9/16	12/21 (57%)
E. Special ovarian cancers	4/12	5/9	9/21 (43%)
Total	15/51 (29%)	37/94 (39%)	52/145 (36%)

TABLE IV

OVARIAN CARCINOMA

STAGE I

UNIVERSITY OF ROCHESTER MEDICAL CENTER 1931–1955

ABSOLUTE 5 YEAR SURVIVAL

Classification	Surgery	Surgery and Irradiation
A. Well differentiated cystadenocarcinoma	4/4	2/5
B. Poorly differentiated cystadenocarcinoma	1/1	1/2
C. Solid adenocarcinoma	0/1	0/0
D. Endometrial type of adenocarcinoma	1/1	3/3
E. Special ovarian cancers	4/4	2/2
Total*	10/11 (91%)	8/12 (62%)

Status of Five Year Survivors

Alive without recurrence: Surgical Series: 11, 9, 8, 7, 6, 6, 6, 5, 5, 5 years.
Irradiated Series: 24, 22, 20, 18, 15, 11, 7.5, 5 years.

group died of a second primary cancer, *i.e.*, breast carcinoma, rectal carcinoma, carcinoma of the uterus—all established by pathologic proof. The one surgical death was due to a second primary in the lung. Most of the patients lived well beyond 5 years, free of disease. The reason the survival in years is longer for the irradiated group is because of the better follow-up of patients in our department.

Stage II. (Table V). Many of the patients in this group were noted to have ruptured ovarian cysts during surgery. Of 9 such patients in the irradiated group, 6 have survived more than 5 years so that this factor is not detrimental in and of itself. Curiously, there were 3 patients with ruptured cysts in the surgery group and only 1 of these patients died with disease, a similar ratio. There is a little weighting of the 2 treatment groups in that most of the poorly differentiated cystadenocarcinoma cases received irradiation (5 of 6 cases). Unlike Stage I cases, most of the patients who died, died with recurrence of their carcinoma. The one long term survivor with disease is a patient with granulosa cell carcinoma who has had repeated surgical and radiotherapeutic procedures. The majority of patients again are long term survivors, living and free of recurrence.

Stage III. (Table VI). Since all patients were referred for radiation therapy, there is no group of cases treated with surgery alone for comparison. The good 5 year survival rate, however, can be attributed to the high proportion of well differentiated cystadenocarcinoma and endometrial carcinoma cases, although some of the cases were solid adenocarcinomas. If we eliminate the 3 survivors beyond 5 years who

TABLE V

OVARIAN CARCINOMA

STAGE II

UNIVERSITY OF ROCHESTER MEDICAL CENTER

1931–1955. ABSOLUTE 5 YEAR SURVIVAL

Classification	Surgery	Surgery and Irradiation
A	2/2	2/3
B	0/1	4/5
C	0/2	0/2
D	2/2	3/3
E	0/0	3/4
	4/7 (57%)	12/17 (70%)

Status of Five Year Survivors

Alive without recurrence: Surgical Series:
11, 7, 6, 5 years.
Irradiated Series: 18, 16, 15, 9, 9, 8, 7, 5 years.
Dead without recurrence:
Irradiated Series: 9, 9, 7 years.
Alive with recurrence:
Irradiated Series: 13 years.

developed recurrences, the survival figure without disease is reduced to 44 per cent. Most of these patients are living and well beyond 10 years and include 3 endometrial type of adenocarcinomas and 1 each of the other types excluding special tumors. Of particular interest is that all of the 5 year survivors had *gross surgical removal of the major mass* with irradiation of disease described as considerable residual in the cul-de-sac and pelvis. Many cases had numerous small implants scattered throughout the bowel, mesentery and omentum which were in the pelvis. All deaths were due to recurrent carcinoma and the more aggressive and fatal cancers were usually solid adenocarcinomas.

Stage IV. (Table VII). Most of the Stage IV cases of any series are hopelessly advanced and, when one considers the extensive disseminated abdominal disease at operation, it is incredible that long term survivors free of disease exist. The surgical group has only one survival. As a rule these patients are too debilitated to receive radiotherapy. The better survival figure in this stage for the irradiated group is due to case selection. Histologic classification is of particular importance in that half of the 5 year survivors are again cases of well differentiated cystadenocarcinomas, and 3 of the 4 long term survivors without disease are of this group of patients. Only 1 of the irradiated 10 year survivors free of disease is a patient with solid adenocarcinoma. Whether irradiation can be credited for the survival can be debated. Most patients in this series received a minimum tumor dose to the *pelvis only* of 2,400 r to 5,000 r in 30 to 60 days with exclusion of upper abdominal metastases in omentum and liver in a number of cases.

Some radiotherapists have indicated that castration may be a factor. Buschke,[5] because of some favorable experiences in widely disseminated serous cystadenocarcinomas, recommends that (1) the pelvis only be treated and the rest of the abdomen omitted regardless of operative findings in the abdomen and (2) the pelvis be treated to a midplane dose of 5,000 r in 6 weeks and increased to 5,500–6,000 r in 8 weeks, if it can be tolerated. Since active menstruation was not a specifically documented item in our initial review of cases, the patients were divided into groups under and above 40 years of age. The survival of those below 40 years was 56 per cent (14/25) and of those above 40 years was 34.5 per cent (38/110). Analyzing the 5 year

TABLE VI

OVARIAN CARCINOMA

STAGE III

UNIVERSITY OF ROCHESTER MEDICAL CENTER

1931–1955. ABSOLUTE 5 YEAR SURVIVAL

Classification	Surgery	Surgery and Irradiation
A	0	3/3
B	0	1/2
C	0	2/5
D	0	3/3
E	0	0/0
Total	0	9/13 (69%)

Status of Five Year Survivors

Alive without recurrence: 17, 16, 11, 10, 10, 5 years.
Alive with recurrence: 5 years.
Dead with recurrence: 14, 5.4 years.

TABLE VII

OVARIAN CARCINOMA

STAGE IV

UNIVERSITY OF ROCHESTER MEDICAL CENTER

1931–1955. ABSOLUTE 5 YEAR SURVIVAL

Classification	Surgery	Surgery and/or Irradiation
A	0/1	4/4
B	0/12	2/28
C	1/10	2/10
D	0/2	0/7
E	0/8	0/3
	1/33 (3%)	8/52 (15%)

Status of Five Year Survivors

Alive without recurrence:
Irradiation: 15, 14, 14, 10 years. Surgery: 5 years.
Alive with recurrence:
Irradiation: 5, 5 years.
Dead with recurrence: Irradiation: 6, 5.3 years.

survivors in this stage, it was noted that 5 patients were menstruating at the time of the initial surgery. Four of the 5 constitute the long term survivors free of disease beyond 10 years in the irradiated group. This is not true of the seven 5 year survivors in Stage III in which only 2 women were actively menstruating at the time of surgery. Of these latter patients, one died 14 years later with recurrent carcinoma and the other has lived 5 years without recurrence.

The only author who reported a program of preoperative irradiation in advanced ovarian carcinoma is Kottmeier.[28] In the year 1958, he routinely treated in this manner patients with poorly differentiated carcinomas (his Class III) in whom complete removal of the cancer was impossible due to peritoneal metastases. Thirty-four of 86 (39.5 per cent) patients were living symptom-free when reported in 1960.

EVALUATION OF OUR RESULTS AND THOSE IN THE LITERATURE

Final conclusions comparing surgical therapy to combined surgical-radiation therapy for carcinoma of the ovary optimally would await a series planned with equal numbers of alternate cases in each stage with the total series having an approximate balance in histologic distribution. In the absence of this, an examination of survival in patients with Stage III lesions would seem the best plausible basis in evaluating the potential usefulness of irradiation in Stage I and II lesions. In both Stage I and II cases for the individual patient, one is always apprehensive as to the extent of microscopic disease not capable of being evaluated surgically. Confusion arises from the uncertainty of a target for irradiation. Peritoneal washings have given objective grounds for apprehensions. Keettel and Elkins[22] reported 5 Stage I ovarian carcinoma patients with no visible break through the capsule, no free fluid in the peritoneal cavity, and no omental or peritoneal implants, yet abnormal cells were present floating free in the peritoneal cavity. For evaluation of the role of irradiation, there is no question of gross residual disease after surgery in Stage III lesions.

Control of Stage III disease, if successful, must be attributed to the radiation therapy, as indeed failure to control the residual disease is undoubtedly ascribed to failure of irradiation. Stage III patients do not have such extensive disease as to make palliation the only realistic alternative and one may reasonably have the objective of control or cure. Furthermore, the disease in Stage III cases is confined to the pelvis where one may give a larger depth dose than one may administer to the abdominal cavity. The clinical situation, therefore, lends itself to reasonable evaluation of the role of irradiation for ovarian malignancy. Stage III patients reported in our series are alive without clinical evidence of disease at 17, 16, 11.3, 10, 10, and 5 years postirradiation, yielding a 5 year survival of 69 per cent. Six Stage III patients have died with disease. If the 2 patients dying with disease after 5 years are counted as radiation failures, it reduces our results to 44 per cent. If the follow-up allows, reports in the literature would be most meaningful if survival were qualified as being *with* or *without* clinical evidence of disease.

Other authors (Table VIII) have had favorable results with Stage III lesions, although there are exceptions.

Carlin and Frodey[6] report 7 Stage III cases treated by surgery alone of which none survived 5 years. Of 7 Stage III cases treated by combined therapy, 3 are reported having 5 year survival.

Gardiner and Slate[15] report 23 Stage III patients treated by surgery alone. The 5 year survival rate was 17 per cent. Twenty Stage III patients were treated by combined surgery and irradiation. The 5 year survival rate was 50 per cent. Gardiner and Slate concluded that radiation therapy definitely increases survival and that differences in the 5 year survival in this group of Stage III cases are significant.

Holme[20] reports only slight improvement in 5 year survival for Stage III lesions with

TABLE VIII

OVARIAN CARCINOMA

STAGE III

FIVE YEAR SURVIVAL RATE

Authors	Surgery Per Cent	Surgery and Irradiation Per Cent
1. Carlin and Frodey[6]	0	43
2. Ellis[13]	None reported	24 (10 year: 20%)
3. Gardiner and Slate[15]	17	50
4. Rubin, Grise and Terry	None reported	*44
5. Holme[20]	12.5	17
6. Kerr and Elkins[24]	None reported	37.2
7. Latour and Davis[31]	23.1	25
8. Munnell and Taylor[40]	0	±36 (graph)
9. Munnell, Jacox and Taylor[41]	0	±28 (graph)
10. Sisson and Garland[53]	None reported	36
11. Kent and McKay[23]	28	53

* Represents those without disease, otherwise 69 per cent.

the use of irradiation. For patients treated by surgery alone, the 5 year survival was 12.5 per cent; for those receiving combined treatment, 17 per cent.

Munnell *et al.*[40,41] in two reports state that the 5 year survival rate for Stage III patients treated by surgery alone was 0 per cent. Five year survival with combined therapy is reported as approximately 36 and 28 per cent.

Kerr and Elkins[24] report a 37.2 per cent 5 year survival rate with combined therapy for Stage III patients. Sisson and Garland[53] report 36 per cent 5 year survival and Ellis[13] a 24 per cent 5 year and 20 per cent 10 year survival.

Latour and Davis[31] (cases from 1930–1950) report a 23.1 per cent (3/13) 5 year survival with surgical therapy, and a 25 per cent (4/16) 5 year survival with combined therapy.

Kent and McKay[23] have recently compiled a detailed report with an attempt at statistical analysis. Although it was probably not ideally randomized in prospect, the authors suggest that it is reasonably so in retrospect. The 53 per cent 5 year survival of patients treated with irradiation is almost twice the 28 per cent of those treated with surgery alone in Stage III cases.

The figures quoted are even more impressive when one considers that the laws of natural clinical selection operated in most series. That is, in all probability, the more aggressive the tumor histologically, the shorter the history of onset and the more rapid the progression, the more likely the case is to be referred for radiation therapy. Only in advanced Stage IV cases are the debilitated patients not given therapy and the surgery alone group would be poorer prognostically. To deny patients with unresectable gross residual pelvic tumor radiation therapy on the basis of available data can hardly be justified.

WHAT CONSTITUTES ADEQUATE RADIATION THERAPY?

A. CONSIDERATION OF PHYSICAL FACTORS

It may not be the modality but the method in which it is used that may account for the failures. Before one abandons a modality of therapy, it is essential to define the treatment factors. In 40 per cent of the articles reviewed the essential factors as to quality and dosage of irradiation were not presented; air or skin doses rather than tumor doses are frequently given. Most publications in the past decade, however, have been co-authored by radiotherapists

and treatment plans have been more detailed.

1. Dose-Time Relationships. There is very little agreement in the literature as to the ideal dose-time relationships. The published data relating to radiation techniques can be divided into three groups: low, moderate, and high dose schedules.

(a) Low Dose Schedules: <2,000 r

The dose given in many series would be regarded as inadequate by present day standards. The reason for the low doses utilized is probably threefold. First, most ovarian carcinomas present as Stage III or IV lesions, involve large portions of pelvic contents and often all viscera of the abdominal cavity. Tolerance to irradiation is poor in such situations and fractionated low dose schedules are often the only alternative. Secondly, there is a certain radiobiologic basis for low doses in that ovarian tumors can be extremely sensitive since the tissue of origin, *i.e.*, the normal ovary, is a very radiosensitive organ. Thirdly, the role of ablation of normal hormonal function of the ovaries, particularly in serous adenocarcinomas, has never been clearly resolved.

The principal protagonist for low to modest dose schedules is Kottmeier.[26] It is his feeling that giving large doses may be detrimental in attaining the desired effect. He prefers to give a series of modest doses over several portals rather than to administer extensive doses which will influence the general condition unfavorably and cause diarrhea and anemia. In cases radically operated upon with gross removal of tumor, 3 or 4 series of roentgen therapy are given toward 2 large anterior and posterior portals—400 r toward each field. This dose is adequate for borderline malignancies, but if a carcinoma with stromal invasion is present, 2 repeat series of 400 r toward the same portals are administered, 3 and 6 months after the first course. If ascites is present, larger opposed abdominal fields receive 1,500 r in 10 to 15 divided doses. For obviously advanced abdominal metastases, a similar modest treatment schedule is used preoperatively. Intrauterine radium therapy is also given whenever possible in all his cases, independent of staging.

In a detailed analysis of their data, Freed and Pendergrass[14] determined that a tumor dose of 1,500 r was a minimum adequate dose. The difference in survival was 47.2 per cent versus 25.8 per cent in patients receiving more than 1,500 r as compared to those receiving less. The authors concluded, however, that the maximal tumor dose rather than the minimal should be used whenever possible.

(b) Moderate Dose Schedules: 2,000–4,000 r

Although doses cover a large range in any one series, most authors prefer doses in the moderate range. The fractionation usually is over 4–6 weeks with daily doses of 150 r–200 r. Of recent authors, Kent and McKay[23] reported good results with doses of 1,400–2,600 r to the midpelvis, but no comment as to the desired dose was made. Latour and Davis[31] favored a dose of 3,000 r to the tumor. Munnell and Taylor[40] worked in a range of 3,500–4,000 r as did Randall and Hall.[47] Those authors who indicated the 4,000 r level as most desirable include Chu,[7] and Kerr and Elkins.[24] Although Ellis[13] and Holme,[20] both British radiotherapists, advocate doses of 3,000–3,500 r with external therapy, supplementation in the form of intrauterine radium is advised, bringing the dose in the center of the pelvis to high levels.

Tod[57] defined the two possibilities affecting time-dose relationships in ovarian carcinoma: (1) treatment of the smallest possible volume of tissue which can be regarded as likely to contain the whole tumor and this can be irradiated to the highest dose which the local tissues can tolerate; or (2) treatment of the whole region likely to be involved by tumor and the most probable site of secondary metastases. In this circumstance, the peritoneal cavity must be treated with moderate dose levels. If one chooses the latter plan as Tod does, then treating the entire abdomen through a

bridge technique is the approach. Daily doses must be small, beginning at 35 r and increased by 5 r daily to each field until 80 r per day is reached. If the white blood cell count stays above 2,000 and monocytes do not drop below 300, a total dose of 3,000 r in 28–30 days is delivered.

(c) High Dose Schedule: 4,000–6,000 r

With the advent of supervoltage radiation, more radiotherapists are delivering a minimum dose of 4,000 r to the pelvis and often up to 5,000 to 6,000 r, depending on response and tolerance. The majority of epithelial ovarian adenocarcinomas are considered radio-responsive or radio-resistant but not sensitive to irradiation. Such schedules are suggested by Munnell *et al.*,[41] Murphy,[42] and those authors who combine external irradiation and intrauterine radium. Even Kottmeier[27] in a recent personal communication stated that he favors doses of 4,000–5,000 r for the pelvis. Nearly all radiotherapists who responded to the questionnaire on the treatment of ovarian carcinoma utilize doses above 4,000 r. Forty per cent of the therapists used doses from 4,000 to 5,000 r and the remaining 60 per cent favored 5,000 to 6,000 r usually in 6 to 8 weeks. It should be recognized that this only applies to pelvic irradiation and when the disease is confined to the pelvis.

When fields include the entire abdomen, most treatment plans aim for levels of 2,000–3,000 r, usually in 6 to 8 weeks. These doses are within bowel tolerance although daily doses seldom can exceed 100 r without causing some gastrointestinal discomfort or distress. Occasionally, depth doses of 150 r are tolerated. The major consideration is renal tolerance which has been defined by Kunkler *et al.*[30] Unless one-third of the total volume of both kidneys can be excluded, doses of 2,300 r will lead to a high incidence of renal failure. Since the whole of both kidneys must be included, one must recognize that even protracted schedules up to 3,000 r and certainly beyond this level are calculated risks, particularly if one achieves a good result and long term survival follows. More than half of the radiotherapists utilizing abdominal irradiation however, advocated doses of 3,000 r or above despite this risk.

2. *Quality of Radiation.* With few exceptions, most of the recorded information is based on orthovoltage techniques employing 200–300 kv. irradiation, half value layer of 1.0–3.0 mm. Cu. Chu[7] was an early advocate of supervoltage irradiation using a 1 mev. unit with a half value layer of 3.4 mm. Pb and more recently Munnell *et al.*[41] have reported schedules for 2 mev., half value layer of 9.0 mm. Cu. Supervoltage therapy is for those radiotherapists who feel that moderately high to high dose schedules are desirable. The physical advantages of skin sparing, higher depth doses, lack of differential bone absorption and less side scatter are immediately apparent. As major centers develop supervoltage techniques, more ovarian cancer patients will be thus treated. In fact, all responses to the questionnaire favored supervoltage over orthovoltage therapy. In no published data is it suggested that supervoltage therapy is superior but this may eventuate because larger doses are delivered more uniformly to the pelvis.

3. *Volume.* Most therapists treat the pelvis with an angulated four portal arrangement using 10×15 cm. fields. Opposed large anterior and posterior portals are also commonly used in this situation with fields measuring 15×15 cm. to 20×20 cm. For abdominal irradiation larger ports are required. Portals measuring at least 30×30 cm., if not larger, must be employed if one wishes to include the contents from the pelvic floor to the diaphragm. The limiting factors in therapy are renal tolerance, followed by bowel and bone marrow damage. Recommendations regarding dosage tolerance in regard to these systems have been covered.

4. *Intrauterine Radium.* No American radiotherapist in response to the questionnaire advocated routinely leaving the uterus behind as a source of radium implantation. The main proponents of this

approach are our British and European colleagues—Kottmeier,[26] Lederman,[32] Dalley[9] and Ellis.[13]

B. CONSIDERATION OF BIOLOGIC FACTORS

An attempt will be made to present the various ovarian malignancies in their order of radioresponsiveness based on clinical experiences as recorded in the literature and on the recent answers to the questionnaire sent to therapists. Radiosensitivity was defined in the questionnaire as being based upon the amount of tumor regression for a similar dose delivered to a similar size mass.

1. Radiosensitivity of Different Tumors Based on Clinical Experience.

(a) *Dysgerminomas.* There is universal agreement that this is the most sensitive ovarian tumor. The counterpart to this tumor in the testes is the seminoma, an equally sensitive lesion. Reports have varied as to the true malignant nature of this tumor with recent 5 year survival figures ranging from 27.1 per cent to 75 per cent. Unilateral oophorectomy followed by partial irradiation of the pelvis with low doses still has its strong advocates.* More often irradiation is routinely advised to whole pelvis after radical hysterectomy and bilateral salpingo-oophorectomy. According to Pedowitz *et al.*,[46] the recurrence rate in encapsulated tumors is lowered and the survival rate is increased from 43.7 per cent at 5 years with irradiation as opposed to 30.8 per cent without radiation therapy. There were no survivors of patients with unencapsulated tumors unless irradiation was employed, resulting in a 23.1 per cent 5 year survival rate.

Although doses recommended have been as low as 600 r favored by Santesson,[49] and Kottmeier,[26] most suggest levels ranging from 1,500 r to 3,000 r. From experience with seminomas, this range, particularly the upper limit, would appear to be satisfactory. With bulky pelvic tumors, response and tumor regression should be one's guide and levels of 5,000 r or more may be necessary to effect complete regression in highly fractionated doses over 2 to 3 months. Actinomycin D potentiation has been tried by D'Angio[8] with some success. With the present knowledge of genetics, attempts to preserve function and to deliver tumoricidal doses to the opposite ovary, a common metastatic or multiple foci site, is not recommended.

(b) *Granulosa Cell Carcinomas.* The paradox of the normal granulosa cell being extremely sensitive whereas its tumor derivatives may be quite radioresistant is difficult to resolve. This observation was made by Studdiford[55] in a case he treated with intrauterine radium and again by Schulze.[51] Traut and Marchetti[58] concluded that roentgen therapy does not effectively retard the growth of granulosa cells. Kent and McKay[23] were doubtful of the radiosensitivity of this tumor. Despite these discouraging observations, there are numerous reports to the contrary, stating that the evident radiosensitiveness of granulosa cell tumors is similar to that of ordinary ovarian follicles. Novak,[43] Dockerty,[11] Klaften,[25] and Dworzak[12] claim that these tumors respond readily to irradiation.

In a review of granulosa cell carcinomas with special reference to their radiosensitivity, Moreton and Leddy[37] try to find a zone of mutual agreement in the reports in the literature. They state that the secretory part of the granulosa cells is radiosensitive in both tumorous and normal ovaries and is destroyed by low doses. The neoplastic tendency of the cells is not destroyed, hence the recurrences and necessity for larger doses.

Kottmeier[26] distinguishes a sarcomatous type of granulosa cell tumor, which carries a higher recurrence rate (71.4 per cent), particularly between 5–10 years after surgery, from the folliculoid or cylindroid type (22.2 per cent recurrence rate). It is his conviction that these lesions are often

* The reasons for unilateral oophorectomy and partial pelvic irradiation are well presented in a recent report published from the Radiumhemmet by Brody. The disparity between the high survival figure of 75 per cent obtained by this conservative approach as compared to other institutions is traced to three factors: the careful selection of pure dysgerminoma cases, the consistent application of postoperative radiotherapy, and the routine of regular follow-up examinations at short intervals. (Brody, S. Clinical aspects of dysgerminoma of the ovary. *Acta radiol.*, 1961, *56*, 209–230.)

radiosensitive and should be treated by radiation.

In summarizing the literature on granulosa cell ovarian tumors, it is noted that most authors have treated granulosa cell carcinomas with modest doses by using intrauterine radium or external irradiation. Even Moreton and Leddy's[37] recommendation of 540 r surface per field to each of 2 anterior and posterior fields can hardly be considered more than low dose therapy effective only in an extremely sensitive tumor. There is sufficient evidence to conclude that granulosa cell tumors are moderately radiosensitive, more so than epithelial tumors such as serous cystadenocarcinomas. It should be recognized that bulky recurrent tumors are poorly oxygenated and will not respond to irradiation as readily as cellular deposits after surgery or implants the size of normal ovaries. However, their growth can be arrested with varying degrees of regression and allow for long survival with residual but inactive tumor.

(c) *Cystadenocarcinomas, Serous versus Mucinous.* Many impressions exist as to the radiosensitivity of cystadenocarcinomas but few observers have attempted to report these. Of 25 investigators referred to earlier only 25 per cent expressed some opinion as to radioresponsiveness. From a pragmatic point of view, there are two general criteria that are used to determine the responsiveness of a tumor to irradiation: first, the dose required to produce tumor regression in regard to the tolerance of surrounding vital structures. If the dose is low or modest, the neoplasm is radiosensitive; as it approaches tolerance it is radioresponsive; and if it exceeds threshold doses of normal tissues it is radioresistant; and secondly, the survival rate is often used as an index of responsiveness since it is reasoned that the only test of response is cure or ablation of the cancer and thereby the survival of the patient. In brief, radiocurability is substituted for radiosensitivity.

Freed and Pendergrass[14] feel that the histologic type does not appear to be of any real value in determining radiosensitivity. Most authors who did not mention the histologic type and radioresponsiveness recommend irradiation, implying comparable sensitivity of serous and mucinous carcinomas.

In published reports, the use of survival as an index of the responsiveness of the tumor offers no solution to the problem; *i.e.*, most authors advocating postoperative therapy obtain better survival for mucinous cystadenocarcinomas as opposed to serous cystadenocarcinomas. A smaller number shows no difference in survival or a more favorable outcome in serous carcinoma. On this basis, one might conclude that mucinous tumors are more radiosensitive than serous tumors.

Specifically stated rather than implied opinions usually indicate mucinous carcinomas as being more radioresistant. Henderson and Bean[17] single out mucinous carcinomas as particularly radioresistant. Kent and McKay[23] on the basis of a comparison of the surgical versus their postoperatively irradiated group of cystadenocarcinomas note no improvement in mucinous cancers and therefore feel that they are not as radioresponsive as serous tumors.

The only statement regarding grading and radiation response is made by Allan and Hertig[1] (Table IX). In general, these authors conclude that the more anaplastic a tumor, the greater its susceptibility to irradiation. The validity of this observation is difficult to substantiate when one examines their data. In comparing the results in different grades of ovarian carcinoma utilizing surgery alone and surgery and

Table IX

Relation of Grading to Radiation Response*

	Per Cent 5 Year Salvage		Per Cent Improvement
	Surgery Alone	Surgery and Irradiation	
Grade 1	58	76	31
Grade 2	32	47	47
Grade 3	2	19	85

* From Allan and Hertig.[1]

radiation therapy,[1] they note an improvement in results in Grade 1 carcinomas of 31 per cent, in Grade 2 carcinomas of 47 per cent, and in Grade 3 carcinomas of 85 per cent with the addition of irradiation. It would appear that the reason the percentage improvement is so large in Grade 3 carcinomas is that the survival of patients treated by surgery alone is poorer rather than that irradiation is so much better. Equating radiosensitivity and percentage improvement as they have done is fraught with error since the yardstick is what surgery alone can do rather than responsiveness to a given dose which can be applied to all tumors.

Observations based on personal experience and correspondence with other radiotherapists would suggest that serous carcinomas are more sensitive than mucinous ones. Regression of serous lesions will occur with doses under 3,000 r–4,000 r, whereas mucinous lesions require more than this. Analysis of our data would substantiate Kottmeier's[26] observation in regard to the degree of differentiation and radiosensitivity of cystadenocarcinomas. The more well differentiated serous tumors respond better than the poorly differentiated lesions, as evidenced by studying our survivors in Stage III and IV cancers. A major number of our long term survivors were those with extremely well differentiated serous carcinomas treated with modest dose schedules. There is no evidence in this series that this holds true for mucinous carcinomas.

(d) *Solid Adenocarcinomas.* Chu[7] states that all adenocarcinomas of the ovary, cystic or solid, are radioresistant and require heavy doses of irradiation. Kent and McKay[23] and Henderson and Bean[17] rate solid anaplastic adenocarcinomas between serous and mucinous cystadenocarcinomas. This seems to be the general impression based on personal communications with other therapists although this was quite variable. Some rated this type of carcinoma more radiosensitive than cystadenocarcinomas, others felt it was more radioresistant. From a pragmatic standpoint, this type of carcinoma must be treated to tolerance and requires doses of 5,000 r–6,000 r to obtain effective regression. The difference in sensitivity between solid and cystadenocarcinomas is too small and variable to be of practical clinical significance.

As in cystadenocarcinomas, solid carcinomas will vary in their response according to tumor bulk. The tumors of large size are poorly vascularized and oxygenated and therefore independent of histology, do poorly or respond sluggishly. One of the reasons offered for using lower schedules for abdominal and peritoneal implants is that implants are better supplied with vascularity and nutrients. Likewise, seedling or individual cells may respond to lower doses given by radiogold administration since they are more susceptible to radiation.

(e) *Endometrial Type of Adenocarcinomas.* This type of adenocarcinoma resembles endometrial carcinomas histologically and commonly arises in endometrial cysts or endometriosis. As Dockerty[11] has noted, adenoacanthomas fall into this group. The curious fact about this tumor type is the relatively high 5 year survival of 57 per cent in our series and 65 per cent in the Mayo Clinic experience. Comparable to this report is that of a group of cases Kottmeier[26] refers to as "cancer uteri et ovarii" in which it is impossible to state whether the entity arose primarily in the ovary or endometrium of the uterus. This constituted a sizable number or 18.6 per cent of all cases of microscopically verified cancer of the ovary. In cases where the ovarian cancer was completely removed surgically, the 5 year survival was 53.5 per cent as opposed to 20.5 per cent in cases in which operation was incomplete.

It is difficult to place this lesion in a definite order of radiosensitivity in regard to the other ovarian cancers. If one assumes that it is similar to endometrial carcinomas, it should be of the same radioresistance as the usual epithelial ovarian cancer.

(f) *Other Malignant Ovarian Tumors.* Experience with most other tumors is too

sketchy to allow for conclusions as to radiosensitivity. Arrhenoblastomas would be expected to have the same radiosensitivity as granulosa cell tumors according to Kottmeier.[26] Experience with this tumor is too limited to make any accurate prediction. Mesonephromas are considered very malignant and not very radiosensitive. Teratomas, teratocarcinomas and choriocarcinomas either alone or mixed with dysgerminomas carry a prognosis akin to their counterparts in the testes. Carcinosarcomas and sarcomas of the ovary proved to be very aggressive and quite radioresistant in a few encounters with these tumors. Krukenberg tumors usually are metastatic from stomach, bowel, and pancreas and rarely are worth treating even for palliative purposes since they are quite lacking in radioresponsiveness.

2. Radiosensitivity of Different Tumors Based on Derivative Cell (Table x).

One of the interesting aspects of ovarian tumorigenesis is determining the cell of origin of different malignancies. Authors have traced cells to the stages of ovarian embryogenesis and have offered elaborate classifications. This information may be helpful in predicting whether tumors would be radiosensitive or not by determining the order of radioresponsiveness of the derivative cell.

The germ cells and their analogue give rise to a number of tumors akin to those of the testes. It is the embryonic primordia of primitive gametogenic cells that are believed to be the cells of origin of dysgerminoma in the ovary or the analogous testicular tumor, the seminoma. Accordingly, the extreme sensitivity of these potential ovogonia in the normal ovary is reflected in the similar sensitivity of dysgerminomas. As the normal ovocyte develops, it becomes more resistant to irradiation. Teratocarcinomas, although derived from germ cells, have matured and have differentiated considerably and as one would expect are quite radioresistant.

The granulosa cell is highly radiosensitive in the developing and mature follicle. On this basis, granulosa cell carcinomas can be expected to be quite radioresponsive. The same is not true of arrhenoblastomas. Parts of these tumors are believed to be derived from potential Sertoli-like cells similar to those in the fetal testes. These are stromal elements and are much more radioresistant than granulosa cells. The masculinizing effects are probably derived from Leydig type cells which are usually found in the hormonally active arrhenoblastomas.

Of particular interest is the derivation of epithelial carcinomas. Most pathologists[2,42] agree that they arise from the surface

TABLE X

OVARIAN CARCINOMA
CONSIDERATION OF BIOLOGIC FACTORS

Embryologic Anatomy	Adult Histology	Malignant Tumor	Radiosensitivity
Primitive germ cell	Totipotential germ cell	Dysgerminoma	Sensitive
	Oocytes and ova	Teratocarcinoma	Resistant
Celomic epithelium	Peritoneum	Serous carcinoma	Responsive
		Mucinous carcinoma	Resistant
Müllerian duct		Endometrial carcinoma	Responsive
		Adenoacanthoma	Responsive
		Solid carcinoma	Responsive
Primitive mesenchyme of urogenital ridge	Granulosa cell	Granulosa cell carcinoma	Sensitive
	Sertoli cell	Arrhenoblastoma	Responsive
	Leydig cell	Masculin ovoblastoma	Resistant
Mesonephros	Mesonephric elements	Mesonephroma	Resistant
Varied	Nonovarian	Krukenberg tumor	Resistant

celomic epithelium covering the normal ovary. The celomic epithelium gives rise to the müllerian duct which in females gives rise to the genital tract organs, *i.e.*, fallopian tubes, uterus and cervix. Thus, the latent müllerian duct potentialities of the surface epithelium may be awakened and development may produce the formation of cancers of the epithelium of the tubal type (serous), epithelium of the endometrial type (endometriomas), and epithelium of the cervix (mucinous).

The practical importance of this concept is that all epithelial cancers have a common anlage, namely the müllerian duct. One would anticipate a similar degree of radioresponsiveness. This is actually the situation clinically in that recommended time-dose schedules are most often identical for solid and cystic adenocarcinomas of the ovary. This was reflected in the questionnaire responses in that at least a third of the radiotherapists felt there was no appreciable difference in the radiosensitivity of different ovarian cancers. Most therapists who noted an order of radiosensitivity based on tumor regression for a comparable dose, nevertheless advocated the same depth dose for ovarian carcinomas whether they were solid, serous or mucinous. It is our conviction that some minor differences exist between the ovarian adenocarcinomas in regard to radioresponsiveness but for the most part they are from moderately responsive to resistant tumors. We feel that all epithelial cancers should be treated to tolerance with high doses ranging from 4,000 to 6,000 r, depending on the site and amount of residual cancer.

PRESENT PHILOSOPHY AND TECHNIQUES

Surgery is the primary form of treatment in all stages of carcinoma of the ovary. Postoperative irradiation will result in a significant number of long term survivors in inoperable neoplasms confined to the pelvis.

STAGE I

A radical hysterectomy with bilateral salpingo-oophorectomy is recommended in all cases. For poorly differentiated cystadenocarcinomas, solid adenocarcinomas (histologic groups B, C), and dysgerminomas, supervoltage irradiation to the pelvis utilizing a 15×15 cm. rotational field delivering 4,000 r in 4–5 weeks is advised. The dose for dysgerminomas should be lower, *i.e.*, between 2,000–3,000 r.

Rationale. Postoperative irradiation in conservative doses is recommended in aggressive histologic types since the chance of pelvic recurrences is believed to be higher.

STAGE II

A radical hysterectomy with bilateral salpingo-oophorectomy is recommended in all cases to be followed by postoperative irradiation. For all histologic types, supervoltage irradiation to the pelvis is again advised, utilizing a 15×15 cm. portal opposed or rotational, to deliver 4,000 r in 4–5 weeks. Isotopic instillation is favored in ruptured cysts, preceding external irradiation in poorly differentiated and solid adenocarcinomas, histologic types B and C, in the form of 100 mc of Au^{198}. Periaortic lymph node irradiation is suggested in dysgerminomas.

Rationale. Since 30 to 50 per cent of ovarian malignancies recur in this stage, postoperative irradiation is again recommended. Microscopic nests of tumor deposited during surgery are more likely to seed and take root at the seams of operative sites than the intact peritoneal surface. Pelvic irradiation is more valuable than isotopic solutions since most cancers recur in the pelvis. It should be stressed that the presence of free floating malignant cells does not constitute an ominous sign. Our past experience and that of others[41,59] show that the majority of such patients live beyond 5 years free of disease whether or not they receive postoperative external irradiation.

STAGE III

As complete removal of as much tumor as possible including a hysterectomy and

bilateral salpingo-oophorectomy is advised. With extensive tumor in the cul-de-sac, the uterus may be utilized for radium implantation. The mainstay of therapy is the supervoltage technique as described, with the exception that large opposed stationary fields up to the umbilicus are employed. The dose is increased to 5,000–6,000 r in 5 to 8 weeks. Daily tumor doses of 150 to 200 r are usually well tolerated. Field size of 15×15 cm. is used and may be reduced as treatment progresses.

All cases receive this therapy regardless of histologic type. Isotopic instillation is recommended in the form of 150 mc of Au^{198}, if ascites is present. If only a biopsy was done and masses were left behind and a dramatic response to radiation treatment occurs, a second operation is strongly urged in 4–6 weeks.

Rationale. Large depth doses to tolerance levels are advocated if the disease is confined to the pelvis. Isotopic therapy is usually advocated since ascitic fluid and scattered cells throughout the abdominal cavity are invariably present. Occasionally, inoperable situations can be made operable and removal of residual tumor foci is possible.

STAGE IV

Often a biopsy is all that can be done but removal of as much tumor bulk as possible is advocated, *i.e.*, huge omental masses of tumor, large cystic masses, etc. The portal arrangement is a pelvic field within a larger total abdominal field measuring 30×20 cm. Supervoltage radiation is preferred with daily doses to pelvis and abdomen in the ratio of 2:1; more commonly 150 r:75 r or 200 r:100 r if tolerated. The dose is usually 5,000–6,000 r to the pelvis and 2,000–3,000 r for the entire abdomen. The kidneys are shielded from the posterior port at 2,000 r so that the dose of these organs seldom exceeds 2,500 r. The course is usually fractionated to 6–8 weeks. In the presence of large tumor masses, a radioactive isotope is generally ineffective. Recently, chemotherapy in the form of actinomycin D is being utilized with irradiation to potentiate the effects of the irradiation. General supportive care is essential and attention to the hemogram and electrolyte balance is necessary.

Rationale. The difference in doses to the abdomen as opposed to the pelvis is determined by tolerance factors. Although implants high in the peritoneal cavity may be more radiosensitive than large pelvic masses, it is doubtful that the doses mentioned are tumoricidal except in rare instances, *i.e.*, well differentiated serous cystadenocarcinomas. Radiation enhancement by chemotherapy is worth considering in all cases. The indirect role of castration in well differentiated serous cystadenocarcinomas remains a possible factor in causing resolution of abdominal metastases.

FUTURE RECOMMENDATIONS

It is obvious that no one institution or author can gather within his lifetime enough cases to formulate a statistically valid opinion as to whether postoperative irradiation is worthwhile. The division of cases into different subgroups further reduces the number of cases to meaningless levels. Nevertheless, an anatomic-histologic classification is essential in order to intelligently interpret the survival data in ovarian cancers. As newer methods are tried, the problem of finding a control group as a yardstick will be everpresent.

The following recommendations seem in order:

1. A standardized dual classification of anatomic and histologic factors as a criterion so that the reported results are uniform.

2. An organized cooperative study among major centers so that different treatment methods may be explored and a sufficient number of cases may be gathered in a reasonable period of time.

These recommendations[34] are not unique but must be re-emphasized if progress is to be made in the next decade in cancer therapy.

TABLE XI

OVARIAN CARCINOMA

ALL CASES

ABSOLUTE 5 YEAR SURVIVAL ACCORDING TO STAGE (PER CENT)

Stage	Rubin, Grise and Terry	Kottmeier[28]	Kent and McKay[23]	Latour and Davis[31]	Munnell, Jacox and Taylor[40]	Carlin and Frodey[6]	Gardiner and Slate[15]	Randall and Hall[47]	Kerr and Elkins[24]	Freed and Pendergrass[14]
I	78	75	53	76	63	62	73	63	52	71.4
II	67	70	59	60	27	52	30	45	42	50
III	44	34	40	24	12	18	32.5	40	37	25
IV	10	9	10	6.7	1.7	0	0	12	4	21
Total	36	35	36	37	28	23	32	28	31.5	39

SUMMARY

1. Ovarian carcinoma is a disease process of late diagnosis and grave prognosis since the majority of patients present as Stage IV cases.

2. Major improvement in survival statistics lies in earlier detection rather than improving existing radiotherapeutic techniques.

3. Evidence of the curative value of postoperative irradiation is offered by the 44 per cent 5 year survival free of disease in our Stage III patients with grossly inoperable tumor limited to the pelvis.

4. Similar experiences reported by other authors are also presented (Table XI).

5. An analysis of unpublished opinions regarding dose, time, volume and quality factors suggests that a more aggressive radiotherapeutic approach to malignant ovarian neoplasia currently prevails in most cancer centers.

6. A clinical and radiobiologic basis of radiosensitivity of different tumors is offered on the basis of derivative cells in ovarian embryogenesis.

7. A philosophy and detailed technique of treatment are suggested.

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IS PRESERVATION OF THE UTERUS WORTHWHILE?*

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THE problems of dealing with malignant disease in any site are great, but malignant tumors of the ovary present special difficulties for three reasons: (1) the insidious nature of the disease; (2) the comparative radio-insensitivity of the lesion; and (3) its rapid and wide dissemination.

Although it is customary to include benign ovarian cysts in any discussion on ovarian neoplasms, the material coming to a radiotherapy department is a selected one in that the diagnosis has almost always been made before the patient arrives. Therefore, only patients with proved primary malignant tumors were included in this series, metastatic ovarian tumors being excluded.

In the years 1945 to 1959, 472 patients with malignant ovarian tumors have been seen at the joint clinic held between the Royal Marsden Hospital and the Chelsea Hospital for Women; of these 288 were previously untreated, 128 were patients with recurrent lesions and 56 had received no treatment (Table I).

TABLE I

MALIGNANT OVARIAN TUMORS
THE ROYAL MARSDEN HOSPITAL, 1945–1959

	Treated	Not Treated	Total
Recurrent	128	24	152
New	288	32	320
Total	416	56	472

When investigating possible etiologic features of ovarian tumors, it is important to elicit the factors common to all patients stricken with the disease. With ovarian neoplasms the main points of interest are: (1) the age group, particularly when related to other malignant tumors affecting women; (2) the marital status of the patients; and, also, (3) their fertility.

Most patients (Fig. 1) were in the 45–64 age group. When comparing the malignant tumors of the breast, cervix uteri, corpus uteri and ovary (Fig. 2), it is seen that the patients in the last two groups have a rather narrow age range, whereas tumors of the breast and cervix uteri may occur in both younger and older age groups.

The majority of patients were married, and a comparison group of similar age as described in the 1951 census shows that there was no undue preponderance of single women. The number of pregnancies in the various age groups when analyzed statistically shows that no definite conclusion can be drawn because of the large number of patients whose pregnancies were unrecorded. There did not appear to be an unusually large number of patients who were either nulliparous or had large families. The 127 nulliparous patients include, of course, most of the 68 single patients.

The symptoms of all types of malignant ovarian tumors, with the exception of those consistent with hormonal effects, are similar. Table II shows the symptoms according to age groups. It is noticeable that in each group the most common symptomatology is related to the abdomen; either abdominal pain or abdominal enlargement. The usual gynecologic symptoms were much less common. This is probably the reason why a large number of patients with this disease are seen and operated on by the general surgeon rather than the gynecologist. Fifty per cent of the patients attended for treatment within 4.4 months of onset of symptoms—the longer delay 5.4 months being

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TABLE II

MALIGNANT OVARIAN TUMORS
THE ROYAL MARSDEN HOSPITAL, 1945–1959
Symptoms According to Age Groups (New Cases Only)

Age	Abdominal Pain	Abdominal Enlargement	Gastro-intestinal Symptoms	Urinary Symptoms	Vaginal Discharge or Bleeding	Back-ache	Enlarged Lymph Nodes	Leg Pain or Swelling	Debility, etc.	Other	Total Known
–44	25 35%	24 33%	5 7%	1 1%	10 14%	2 3%	1 1%	1 1%	1 1%	2 3%	72 99%
45–54	27 28%	31 32%	8 8%	4 4%	14 14%	3 3%	4 4%	2 2%	2 2%	2 2%	97 99%
55–64	24 25%	32 33%	9 9%	5 5%	13 14%	4 4%	2 2%	1 1%	3 3%	3 3%	96 99%
65–	15 25%	18 33%	5 9%	1 2%	7 13%	— —	2 4%	4 7%	1 2%	2 4%	55 101%
Total	91 28.4%	105 32.8%	27 8.4%	11 3.4%	44 13.8%	9 2.8%	9 2.8%	8 2.5%	7 2.1%	9 2.8%	320 99.8%

The % figures show percentage age distribution within each age group. No attempt has been made to round off individual percentages in such a way as to make each total exactly 100%.

in the 45–54 age group where the symptoms of the tumor may be confused with those of the menopause. An "acute abdomen" caused by torsion of an ovarian cyst is unusual because it is common for the malignant tumor to become fixed at a comparatively early stage.

The duration of symptoms and age of the patient both influence the results of treatment. The most favorable survival results (45 per cent at 3 years and 27 per cent at 5 years) followed the treatment of those patients who came within 2 months of the onset of the disease. After even a delay of 9

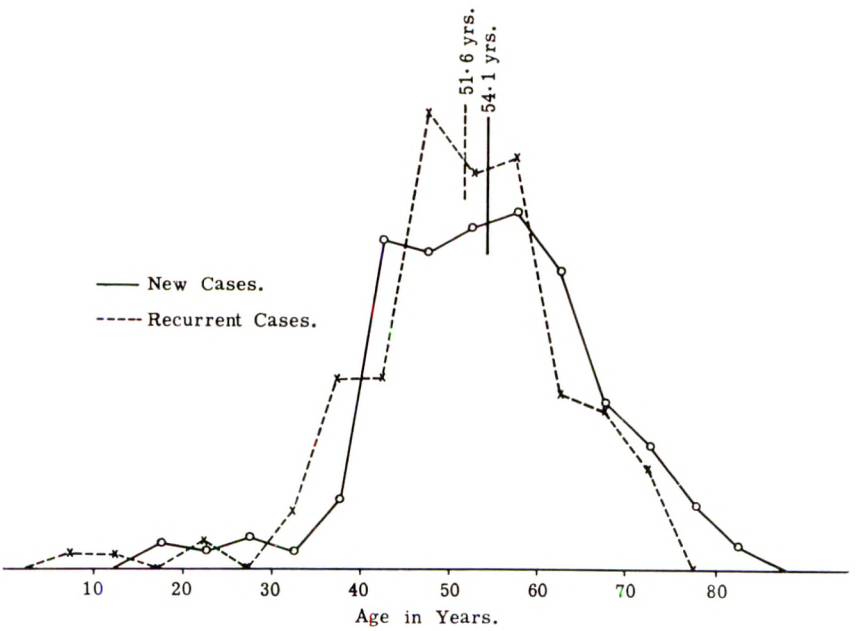


FIG. 1. Age distribution of new and recurrent cases of malignant ovarian tumors. The Royal Marsden Hospital, 1945–1959.

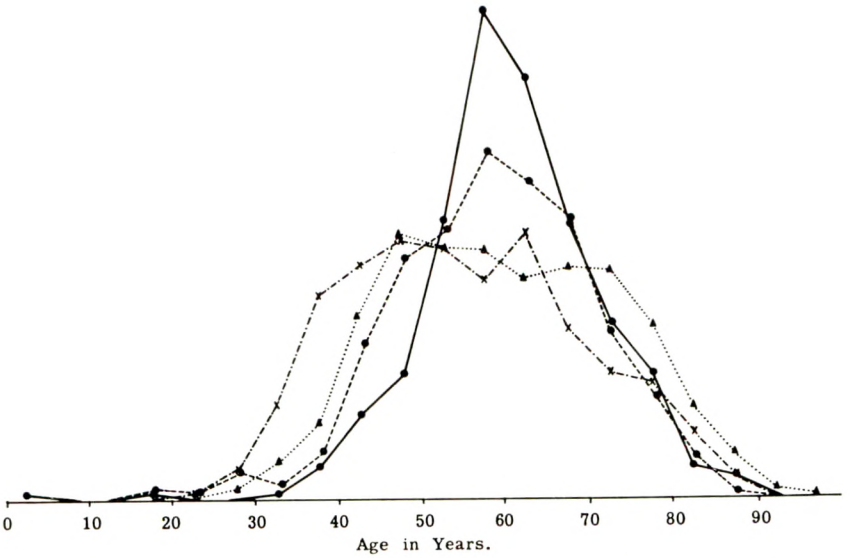


FIG. 2. Comparison of age incidence of malignant tumors of breast, cervix uteri, corpus uteri and ovary. The Royal Marsden Hospital, 1945–1959.

Key:

. . . . . Malignant tumors of breast
–·–·–·–·– Malignant tumors of cervix uteri
———— Malignant tumors of corpus uteri
– – – – – Malignant tumors of ovary

months, the results were 34 per cent and 24 per cent at 3 and 5 years respectively. This was due to the large number of Stage 1 patients in these groups, and emphasized the prognostic importance of the tumor type, since only a slow growing tumor would remain localized for this length of time.

The older age group showed a worse survival rate compared with the younger group even allowing for the difference in natural life expectancy. The 40–50 year group survival rate was 34 per cent for 5 years, whereas for 60 years and over it was only 14.3 per cent—approximately the same number of patients being at risk in each instance.

A. TREATMENT METHODS ADVOCATED

The methods of treatment available are surgery, radiotherapy and chemotherapy, and usually a combination of at least the first two and sometimes of all three is necessary if the patient is to survive any reasonable length of time.

(1) SURGERY

Except under special circumstances, surgery should always be the initial method of treatment, partly in order to establish the diagnosis since neither the size and fixity of the tumor, nor the presence of ascites is absolutely diagnostic of malignancy, and partly because one is dealing with a comparatively radio-insensitive tumor and in general it seems that the survival rate improves if as much of the tumor as possible is removed at operation. The difficult thing to decide is what should be the extent of the surgery: should a macroscopically benign ovary be removed as well as the frankly malignant one; should the healthy uterus be left as a radium container, and should the omentum be removed routinely or only if tumor is present? In view of the number of times a "benign" tumor proves on microscopic examination to have malignant cells present and the frequency with which these tumors are bilateral (32 per cent), there seems no doubt that both ovaries should always be removed at opera-

tion. If the healthy uterus is left behind, radium can be placed in it in order to supplement external radiation. Undoubtedly, spread from the ovary to the uterus can, and does, occur, and if this has obviously happened then the uterus should be removed, but if the uterus appears normal the advantages of supplementing the dose to the pelvis by means of radium would seem greater than the risk of the disease persisting in the uterus.

This is, of course, particularly useful when high voltage therapy (180 kv.–400 kv.) alone is used, but even using supervoltage therapy it is still advantageous to be able to give a rather localized high dose in the region where lesions have a particular tendency to recur. This view is also expressed by Kottmeier.[1]

The omentum is commonly the site of metastasis either by direct or lymphatic spread, and it would therefore have seemed worthwhile removing it. However, recent work from Texas[2] shows that in several cases this was done and the survival rates were not improved, more patients in fact dying from intestinal obstruction than in a control group. It is, nevertheless, worthwhile removing any gross metastasis which might possibly give rise to symptoms later.

(2) RADIOTHERAPY

Because of the spread of the disease, external irradiation is undoubtedly the most important form of radiotherapy. Experience has shown that when the disease has spread outside the pelvis the chances of survival are very small, and that any treatment is purely palliative. It has, therefore, been our custom to treat the pelvis only to a dose of 5,500 r where radium therapy is going to be used subsequently, or 6,000 r if the uterus has been removed. If, however, the disease has spread outside the pelvis, then an attempt is made to treat the upper abdomen as well—the treatment in all areas being usually between 3,000–4,000 r depending on the patient's tolerance. The

TABLE III

MALIGNANT OVARIAN TUMORS
(Excluding Group E)
THE ROYAL MARSDEN HOSPITAL, 1945–1959
Three and Five Year Survival Rates by Stage and Histologic Group

Stage	Term	Histologic Groups												All Groups		
		Group A			Group B			Group C			Unclassified					
		At risk	Known alive	% Survivals	At risk	Known alive	% Survivals	At risk	Known alive	% Survivals	At risk	Known alive	% Survivals	At risk	Known alive	% Survivals
I	3 yr.	10	9	90	4	3	—	2	2	—	8	6	—	24	20	83
	5 yr.	8	7	—	2	1	—	1	0	—	7	5	—	18	13	72
II	3 yr.	16	10	63	15	4	27	12	4	33	10	3	30	53	21	40
	5 yr.	12	8	67	13	2	15	8	1	—	8	1	—	41	12	29
IIs	3 yr.	7	4	—	7	2	—	3	2	—	8	2	—	25	10	40
	5 yr.	6	3	—	5	2	—	1	0	—	6	1	—	18	6	33
III	3 yr.	19	2	11	16	1	6	25	2	8	19	1	5	79	6	8
	5 yr.	9	1	—	7	0	—	12	0	0	15	0	0	43	1	2
IV	3 yr.	5	1	—	8	0	—	13	0	0	1	0	—	27	1	4
	5 yr.	2	0	—	5	0	—	7	0	—	1	0	—	15	0	0
Unstaged	3 yr.	—	0	—	1	0	—	—	0	—	2	1	—	2	1	—
	5 yr.	—	0	—	1	0	—	—	0	—	2	1	—	2	1	—
All new patients	3 yr.	57	26	46	50	10	20	55	10	18	48	13	27	210	59	28
	5 yr.	37	19	51	32	5	16	29	1	3	39	8	21	137	33	24

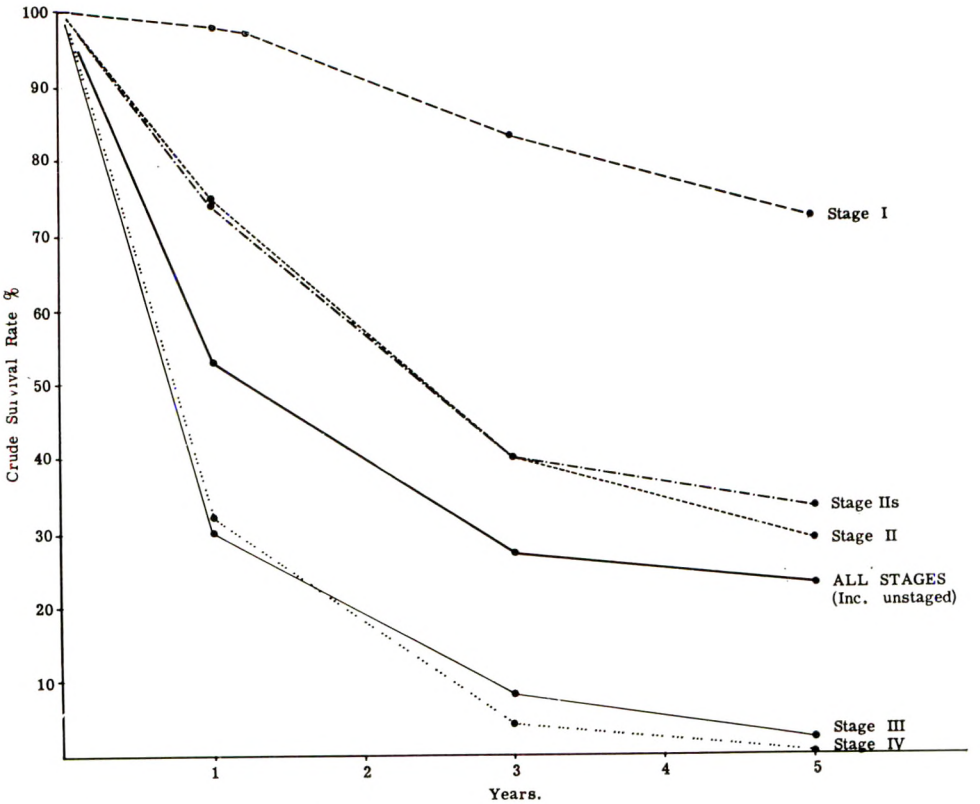


FIG. 3. Results by stage in malignant ovarian tumors. New patients only. Group E excluded. The Royal Marsden Hospital, 1945–1958.

lateral margin of the upper field extends to the pelvis of the kidney, and therefore the kidney itself receives little irradiation. The majority of the patients reported here were treated by roentgen rays at 250 kv., but during the last 5–6 years many were treated by 2 mev. radiation (Van de Graaff).

It is difficult to assess the rightful place of intraperitoneal radioactive colloidal gold. In a few early cases where the tumor was thought to be confined to the ovary and was histologically well differentiated, the only form of postoperative radiotherapy was the instillation of 120 mc of radioactive gold into the peritoneal cavity. However, few of these patients did well, and many of them rapidly developed recurrent disease. At present we reserve this method of treatment for cases of rapidly recurring ascites: the patients should be in good general condition without gross palpable masses in the abdomen or pelvis. The discomfort of the procedure is usually minimal and lasts only 24–48 hours, and in many cases the ascites re-forms more slowly or may even disappear for a few months. It should, however, be emphasized that the treatment is purely palliative and that the patient will inevitably die from the disease within the year or earlier.

Radium is used according to the Stockholm method. The first insertion—50 mg. being placed in the uterus and 40 mg. in the vagina—is made 2–3 weeks after completion of external treatment and certainly not before any proctitis has settled down. A second insertion follows two weeks later; in each case the radium is left in position for 22 hours.

(3) CHEMOTHERAPY

Chlorambucil has been mainly used, usually for patients with disease so advanced that neither radiotherapy nor

radical surgery can offer any prospect of palliation. Some of these have been made more comfortable, and it is a method of treatment worth pursuing. However, most patients who have benefited from such treatment have had high dosage followed by leukopenia. The average initial dose of chlorambucil is 10 mg. daily and after the first month a maintenance dose is given to keep the patient leukopenic. It has now become routine for all patients with carcinoma of the ovary to be seen by the chemotherapist whatever treatment is contemplated so that their general condition and extent of the disease can be noted for the future. If there is disease remaining after surgery and external irradiation, then chemotherapy is given. An attempt has been made to give radiotherapy and chemotherapy at the same time, but the leukopenia was so sudden and severe that the risk has been felt to be unjustifiable. If chlorambucil proves ineffective and the disease is uncontrolled, then endoxan is sometimes of benefit.

Recently, in some of the more advanced cases chemotherapy followed by radiotherapy has been used if the tumor has decreased in size sufficiently to make radical radiotherapy a feasible proposition.

B. RESULTS BY DUAL CLASSIFICATION

The following factors influence the survival rate of these patients: (1) the anatomic extent of disease when the patient is first seen; (2) the histologic type of the tumor; and (3) the method of treatment.

The following staging has been suggested in this symposium:

Anatomic Stage:

I. Tumor limited to ovary, no evidence of microinvasion, completely removed surgically.

II. Tumor shows evidence of microinvasion of capsule, blood vessels,

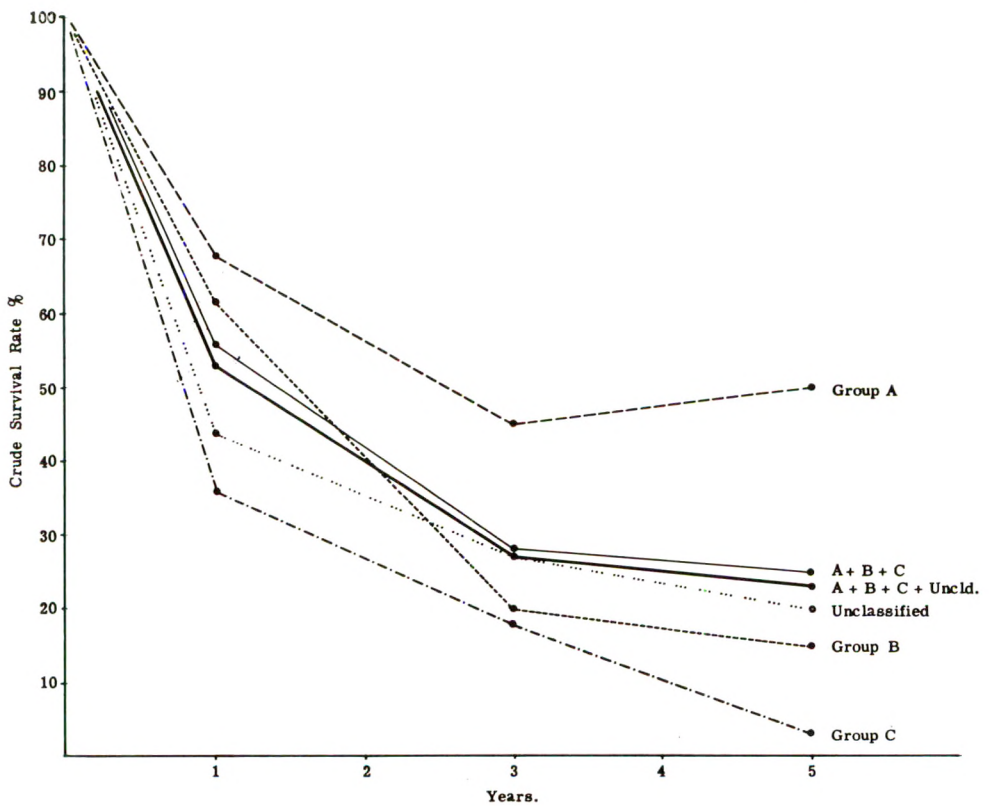


FIG. 4. Results by histologic groups in malignant ovarian tumors. The Royal Marsden Hospital, 1945–1958.

lymphatics, but grossly removed surgically.

II S. Rupture of cystic tumor, grossly removed surgically.

III. Tumor extends into pelvis but not beyond, and is grossly inoperable or gross residual disease left in the pelvis.

IV. Tumor beyond pelvis, lesion inoperable.

Histologic Type:

Grade A. Well differentiated cystadenocarcinoma } includes both serous and
Grade B. Poorly differentiated cystadenocarcinoma } pseudomucinous
Grade C. Solid carcinoma
Grade D. Endometrial type of adenocarcinoma
Grade E. Others (dysgerminoma, granulosa cell carcinoma, arrhenoblastoma, etc.)

If, instead of discussing the effect of stage and histology separately, the two are combined together much more useful information can be gained on their dual influence on survival rates.

(1) ANATOMIC EXTENT

When the available material is classified according to this double method (Table III) there is a marked difference in results at 5 years once the disease has spread through the capsule of the ovary, namely 72 per cent for Stage I, and 29 per cent for Stage II where the capsule has been penetrated. The effect of grading is also dramatic; the results for all stages in the well-differentiated group being 51 per cent at 5 years, dropping to 15 per cent at 5 years for all stages in the undifferentiated group of tumors.

(2) HISTOLOGIC TYPE

For various reasons, details about the histology were not available in some cases and even allowing for these the results are essentially the same: the over-all 5 year survival results in the group including the unclassified being 24 per cent, rising to 26 per cent if the unclassified is excluded. It is easy to improve one's results by including cases of doubtful malignancy. We have endeavored to avoid this and it will be seen that there are only 42 cases in Stage I as compared with 94 in Stage II. Even in the recurrent cases, the influence of histology was obvious, since the only reasonable number of survivals occur in the well differentiated group (Type A) tumors (25 per cent) as opposed to no survivors with Type B and C tumors. Figures 3 and 4 show the effect of staging and histology on results even more clearly.

The natural history of tumors classified in Group E is quite different from the others, and varies from one to the other. In this series the commonest tumors are the granulosa cell tumors which are often comparatively benign. The survival of patients suffering from granulosa cell tumor may be quite long—particularly if surgery is followed by radiotherapy, since they are very radiosensitive. Only 2 patients with arrhenoblastoma were seen—one died within 3 years and the other is alive at 4 years. The results in the 4 cases of teratoma were poor, the only long term survival being a patient with squamous cell carcinoma arising in a dermoid cyst. Seven patients with dysgerminoma were seen: again the survival time was short, only 1 patient surviving for 5 years, although 2 are still alive at 2 and 3 years. The radiosensitivity varies but radiotherapy should be given in an attempt to improve the results.

(3) METHOD OF TREATMENT

The number of cases where surgery was not followed by radiotherapy is small and it is therefore difficult to compare the two groups. Table IV shows the 3 year and 5 year survival rates, respectively. At 3 years the results in the combined therapy group (40 per cent) are distinctly better than in those where surgery alone (32 per cent)

TABLE IV

MALIGNANT OVARIAN TUMORS
THE ROYAL MARSDEN HOSPITAL, 1945–1959

Three and Five Year Survival Rates by Method of Treatment and (a) Stage and (b) Histologic Group

Treatment	(a) Stage	3 Year Results 1945–1956			5 Year Results 1945–1954			(b) Hist. Group	3 Year Results 1945–1956			5 Year Results 1945–1954		
		Number at risk	Known alive	% Survivals	Number at risk	Known alive	% Survivals		Number at risk	Known alive	% Survivals	Number at risk	Known alive	% Survivals
Surgery Only	Unstaged	1	0	—	1	0	—	Unclassified	10	2	—	10	2	—
	I	8	7	—	6	6	—	A	14	9	—	9	7	—
	II	9	1	—	7	1	—	B	8	1	—	4	0	—
	IIs	6	2	—	6	2	—	C	5	0	—	4	0	—
	III	6	1	—	4	0	—	E	—	—	—	—	—	—
	IV	7	1	—	3	0	—							
	Total	37	12	32	27	9	33							
Surgery and Radium and/or External Irradiation	Unstaged	2	1	—	2	1	—	Unclassified	21	11	52	16	6	38
	I	19	15	79	12	7	—	A	33	17	52	24	12	50
	II	46	22	48	36	13	36	B	36	9	25	25	5	20
	IIs	20	9	45	13	5	—	C	30	10	33	15	1	7
	III	36	5	14	18	1	56	E	10	5	—	6	3	—
	IV	7	0	0	5	0	—							
	Total	130	52	40	86	27	31							
Radium and/or Beam Therapy	Unstaged	—	—	—	—	—	—	Unclassified	6	0	—	4	0	—
	I	—	—	—	—	—	—	A	5	0	—	1	0	—
	II	—	—	—	—	—	—	B	—	—	—	—	—	—
	IIs	—	—	—	—	—	—	C	7	0	—	3	0	—
	III	14	0	0	6	0	—	E	—	—	—	—	—	—
	IV	4	0	—	2	0	—							
	Total	18	0	0	8	0	—							
Colloidal Gold Only	Unstaged	—	—	—	—	—	—	Unclassified	2	0	—	1	0	—
	I	—	—	—	—	—	—	A	4	0	—	3	0	—
	II	—	—	—	—	—	—	B	3	0	—	3	0	—
	IIs	—	—	—	—	—	—	C	5	0	—	2	0	—
	III	7	0	—	3	0	—	E	—	—	—	—	—	—
	IV	7	0	—	6	0	—							
	Total	14	0	—	9	0	—							
Untreated	Unstaged	—	—	—	—	—	—	Unclassified	9	0	—	8	0	—
	I	1	0	—	1	0	—	A	1	0	—	0	0	—
	II	—	—	—	—	—	—	B	3	0	—	—	—	—
	IIs	—	—	—	—	—	—	C	8	0	—	5	0	—
	III	17	0	0	12	0	—	E	—	—	—	—	—	—
	IV	3	0	—	0	0	—							
	Total	21	0	0	13	0	—							
Total	Unstaged	3	1	—	3	1	—	Unclassified	48	13	27	39	8	21
	I	28	22	79	19	13	68	A	57	26	46	37	19	51
	II	55	23	42	43	14	33	B	50	10	20	32	5	16
	IIs	26	11	42	19	7	37	C	55	10	18	29	1	3
	III	80	6	8	43	1	2	E	10	5	—	6	3	—
	IV	28	1	36	16	0	0							
	Total	220	64	29	143	36	25							

TABLE V

MALIGNANT OVARIAN TUMORS

THE ROYAL MARSDEN HOSPITAL, 1945–1956

New Cases. Three year survival rates according to presence or absence of hysterectomy and radium insertion as part of initial treatment

Untreated and Group E cases excluded

	Stage	+ Radium Insertion			− Radium Insertion			Total		
		No. at risk	Known alive	% 3 yr. Survivals	No. at risk	Known alive	% 3 yr. Survivals	No. at risk	Known alive	% 3 yr. Survivals
+ Hysterectomy	I	2	1	—	10	10	—	12	11	—
	II	1	0	—	19	12	63	20	12	60
	IIs	1	0	—	9	5	—	10	5	—
	III	2	1	—	13	2	—	15	3	20
	IV	—	—	—	5	0	—	5	0	—
	Unstaged	—	—	—	1	0	—	1	0	—
	Total	6	2	—	57	29	51	63	31	49
− Hysterectomy	I	2	2	—	9	7	—	11	9	—
	II	16	6	38	17	3	18	33	9	27
	IIs	3	1	—	12	4	—	15	5	33
	III	13	3	—	34	0	0	47	3	6
	IV	3	0	—	16	1	6	19	1	5
	Unstaged	—	—	—	1	1	—	1	1	—
	Total	37	12	32	89	16	18	126	28	22
Total	I	4	3	—	19	17	89	23	20	87
	II	17	6	35	36	15	42	53	21	40
	IIs	4	1	—	21	9	43	25	10	40
	III	15	4	27	47	2	43	62	6	10
	IV	3	0	—	21	1	5	24	1	4
	Unstaged	—	—	—	2	1	—	2	1	—
	Total	43	14	33	146	45	31	189	59	31

was performed, and this is of particular interest because the former group included a larger percentage of more malignant tumor types.

At 5 years, however, there is a less noticeable difference in the results, showing that the effect of radiotherapy in advanced disease is in the main palliative rather than curative.

Tables v and vi show the result of leaving the normal uterus for use as a radium container; at 3 years the results are better in the group where hysterectomy has been performed (51 per cent versus 32 per cent) whereas at 5 years more patients survive whose uterus has been left and radium inserted into it (36 per cent versus 44 per cent).

The practice of not removing the healthy uterus has been carried on for many years at the Radiumhemmet, Stockholm, and it is also customary at the Royal Marsden Hospital since this seems the most efficient way of dealing with pelvic disease. Kottmeier[1] states that recurrences are frequently seen in the pelvis, and therefore recommends sparing the uterus for the application of radium in order to apply a satisfactory radiation dosage to the pelvis. The radium is put into the uterine cavity one week or later following operation. A curettage is done immediately prior to the

TABLE VI

MALIGNANT OVARIAN TUMORS
THE ROYAL MARSDEN HOSPITAL, 1945–1954

New Cases. Five year survival rates according to presence or absence of hysterectomy and radium insertion as part of initial treatment
Untreated and Group E cases excluded

	Stage	+ Radium Insertion			− Radium Insertion			Total		
		No. at risk	Known alive	% 5 yr. Sur-vivals	No. at risk	Known alive	% 5 yr. Sur-vivals	No. at risk	Known alive	% 5 yr. Sur-vivals
+ Hysterectomy	I	2	1	—	8	7	—	10	8	—
	II	1	—	—	14	5	—	15	5	33
	IIs	1	—	—	8	3	—	9	3	—
	III	2	—	—	8	—	—	10	—	—
	IV	—	—	—	4	—	—	4	—	—
	Unstaged	—	—	—	—	—	—	—	—	—
	Total	6	1	—	42	15	36	48	16	33
− Hysterectomy	I	2	2	—	5	3	—	7	5	—
	II	11	5	—	15	2	13	26	7	27
	IIs	—	—	—	9	3	—	9	3	—
	III	4	1	—	17	—	0	21	1	5
	IV	1	—	—	10	—	—	11	—	—
	Unstaged	—	—	—	1	1	—	1	1	—
	Total	18	8	44	57	9	16	75	17	23
Total	I	4	3	—	13	10	—	17	13	87
	II	12	5	—	29	7	24	41	12	29
	IIs	1	—	—	17	6	35	18	6	33
	III	6	1	—	25	—	0	31	1	3
	IV	1	—	—	14	—	—	15	—	0
	Unstaged	—	—	—	1	1	—	1	1	—
	Total	24	9	38	99	24	24	123	33	27

application. A dose of 2,000 to 3,000 gamma r is given to the anterior wall of the rectum. He states that a satisfactory dose could also be given by external irradiation, but this would require the irradiation of a larger volume of tissue with greater discomfort to the patient. The recently reported results of Kottmeier with this method are comparable or slightly better than those of many authors favoring total hysterectomy and no intrauterine radium. (See Table XI of "Has postoperative irradiation proved itself?" by P. Rubin *et al.* of this symposium.)

SUMMARY

1. Because of the small number of cases in this series, one should not be dogmatic about the value of this procedure, but it would seem reasonable to use it until a large number of patients has been so treated.

2. The results in the treatment of this disease are generally so poor that no method which might improve them should be ignored.

The Royal Marsden Hospital
London, England

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TREATMENT OF OVARIAN CANCER WITH RADIOACTIVE ISOTOPES*

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THE treatment of ovarian cancer is a great challenge to whomever comes in contact with this neoplasm, be he surgeon, radiologist, gynecologist, internist, endocrinologist, or general practitioner. The fact that these tumors are so difficult to diagnose often results in a delayed diagnosis with spread of the cancer before the time of operation. Many ovarian cancers are of a cystic nature, and there is frequently rupture of the cysts either spontaneously or as a result of trauma, or during surgery with numerous resultant cancer seedings throughout the peritoneal cavity.

There has been no significant improvement in the last 20 years in the over-all cure rate of ovarian cancer. Most large series report a 5 year cure rate in the vicinity of 30 per cent of all patients treated. This rather dismal figure warrants critical evaluation to note if other methods may be available for treating these neoplasms. The probability that diagnostic measures may improve and that the neoplasms will be diagnosed and treated earlier is not great.

In this presentation the experience with radioactive isotopes in the treatment of cancers arising in the ovary is described. The experience is analyzed and the benefits evaluated in an attempt to formulate treatment policies for the use of this modality in the management of this group of neoplasms. All but 5 of the patients had evidence of widespread carcinoma when they received the isotopes. Their response to the treatment provides a base for determining techniques of delivering radiation from radioactive isotopes.

Eighty patients bearing ovarian cancer have been treated with radioisotopes for one or more of the following reasons: (1) intra-abdominally, as a prophylactive measure after an apparently successful resection of an ovarian cancer; (2) intra-abdominally, for the control of ascites; (3) intra-abdominally, when there was evidence of dissemination of ovarian cancer without ascites; (4) interstitially, into pelvic masses; (5) miscellaneous: intrapleurally, to control hydrothorax; intra-arterially, to determine the effects of isotopes administered into the arterial supply of the cancer; and combinations of these procedures.

AGES OF PATIENTS, HISTOLOGIC TYPES, AND EXTENT OF CANCERS

The ages of the patients, by decades, were as follows:

Decade	*No. of Patients*
0–10	0
10–20	1
20–30	3
30–40	6
40–50	28
50–60	26
60–70	14
70–80	2
80+	0

The histologic diagnosis was:

Cystadenocarcinoma	43
Anaplastic carcinoma	10
Adenocarcinoma	12
Granulosa-cell carcinoma	3
Pseudomucinous carcinoma	1
Teratoma	1
Type of cancer not stated	10

The extent of the cancer in patients of this group was as follows:

Generalized abdominal metastases	60
Metastasis to liver	13
Metastasis to lung	9
Metastasis to cervival lymph	

* From the Radioactive Isotope Service, The Hospital for Joint Diseases, New York, and the Pack Medical Foundation, New York, New York.

	No. of Patients
nodes (signal nodes)	6
Pelvic deposits	7
Metastasis to opposite ovary	5

Evidence of intestinal obstruction was noted in 23 patients. These values are not mutually exclusive inasmuch as a patient may have had generalized abdominal metastases and, in addition, metastasis to the lung, or he may have had evidence of intestinal obstruction.

From this breakdown it will be seen that most of the patients were in the fourth or fifth decade of life; that adenocarcinoma, especially cystadenocarcinoma, was the most common histologic type of cancer; that generalized abdominal metastases were the most frequent condition; and that there was a rather high incidence of intestinal obstruction. Relatively few patients had metastasis to the lung; a few had localized, large pelvic deposits. Five patients presented evidence of involvement of both ovaries only. The observation that most of the patients had generalized intra-abdominal metastases suggests that intra-abdominal isotopes may be effective in combating this form of cancer.

TYPES OF ISOTOPES AND DOSAGES

The three isotopes most frequently used were: radioactive gold (Au^{198}), radioactive yttrium (Y^{90}), and radioactive chromic phosphate ($CrP^{32}O_4$). Combinations of these isotopes were often administered as part of an investigation studying the effects of combining an isotope of short half-life with one of longer half-life. Radiation delivered over a short period combined with more prolonged irradiation seems to have certain advantages. Usually, either radioactive gold or yttrium was administered as the short-lived isotope and combined with radioactive chromic phosphate as the longer-lived isotope. Other isotopes are being investigated as part of this study. Palladium is such an element, with one isotope, palladium 109, having a half-life of $13\frac{1}{2}$ hours, and another isotope, palladium 103, having a half-life of 17 days.

Radioactive gold has a half-life of 2.7 days. The ultramicroscopic colloidal gold particles become condensed within 1 to 2 days into visible, dot-like particles in the cytoplasm of the macrophages, which are probably then mobilized on the mesothelial surface of the serosa, and uniform deposition on the serosal surface is obtained by the intra-abdominal administration of the radioactive gold. Because of the low half-path (0.4 mm.), about 90 per cent of the ionization resulting from the beta particles occurs within the first millimeters of the serosa. This reaction is, accordingly, a superficial one. About 10 per cent of the Au^{198} radiation spectrum is gamma radiation with an energy of 0.411 mev. Radioactive chromic phosphate is a suspension in dextrose of ignited and finely ground chromic phosphate, having a particle size of 0.2 to 0.4 μ. It is not truly a colloid but, rather, a suspension of particles that tend to agglomerate upon contact with the peritoneal fluids and also have a tendency to "puddle" in the lower peritoneal cavity. The long half-life of P^{32} within the chromic phosphate is $14\frac{1}{2}$ days. The dissipation of the radioactivity is considerable; about 2 months is required to deliver 97 per cent of the total energy. Radioactive yttrium (Y^{90}) is a pure beta emitter in the range of 2.18 mev., with a half-life of 61 hours. It forms insoluble complexes with nucleic acids. When given intraperitoneally, it must be administered simultaneously with a carrier—nonradioactive yttrium (Y^{89}). This results in the formation of large molecules when the yttrium combines with proteins, thereby assuring against escape of the yttrium from the abdominal cavity.[11]

The dose varied from 50 to 150 mc of radioactive gold; from 30 to 40 mc of radioactive yttrium; and from 10 to 20 mc of radioactive chromic phosphate. The dose was determined by considering all factors, including the size and weight of the patient, her general metabolic state, the hematopoietic reserve, and previous therapy. If only gold was to be used, the

patients received from 100 to 150 mc of the isotope intra-abdominally; on the other hand, if she was to be treated by a combination of gold and chromic phosphate, she would then receive 50 to 100 mc of gold and 10 to 20 mc of radioactive chromic phosphate.

When the isotopes were administered for the control of fluid, either a paracentesis or a thoracentesis was performed, and the isotopes were administered directly into the abdomen or chest, being diluted by a residual fluid. If the isotopes were administered into a "dry abdomen," *i.e.*, an abdomen known to be the seat of multiple carcinomatous implants but with no ascites, a 15 gauge needle would be inserted into the abdomen under local procaine infiltration, and a small polyethylene catheter would be threaded through the needle. If the catheter went smoothly into the abdominal cavity, it was then known to be in a free peritoneal cavity and not in the abdominal wall, omentum, or a viscus. The isotopes were diluted with 250 to 350 cc. of saline and administered into the abdominal cavity.

At the time of surgery, either for definitive removal of the cancer or for exploratory laparotomy, a polyethylene tube was left in the abdominal cavity for the administration of the isotopes.

When given interstitially, the isotopes were injected in small volume, varying from 1 to 4 cc., into the pelvic masses, the injection usually being made through the vagina. In one instance the technique of Greenberg and Dudley was used, in which radioactive yttrium was incorporated in soluble cellulose strands and delivered through the vagina to a pelvic mass. This was done by Dr. Joseph Greenberg. The procedures were usually performed in the patient's room with local anesthesia, although two interstitial administrations were done in the operating room under pentothal anesthesia. After the administration of the isotopes into the abdomen, the patients were instructed to roll about from side to side for about an hour. Each patient cooperated and a better distribution of the isotopes throughout the abdominal cavity was thus assured.

The dose in rads from isotopes administered interstitially was calculated from the formula

$$D_\beta = 73.8\ C \times E_\beta \times T$$

where D_β is the total dose delivered over the lifeline of the isotope in rads, C is the concentration in μc per gm. of tissue, E_β is the average beta ray energy in mev., and T is the effective life in days. Inasmuch as the isotopes of this experiment can be retained indefinitely in the organ, the effective life is equivalent to the radiochemical mean life. Thus, for Y^{90}, which has a half-life of 2.54 days, with an average beta ray emission of 0.93 mev., 0.6 mc will deliver 1,000 rads beta to 100 gm. spherical organ.

The dose delivered to the peritoneum after intra-abdominal administration is calculated on the basis that the abdomen is 5,000 sq. cm. and utilizing the above formula, 10 mc of $CrP^{32}O_4$ would deliver 21,600 rads beta equivalent.

RESULTS

LONGEVITY

Sixty of the 80 patients treated have died: 58 from ovarian cancer, one from a cerebrovascular accident, and one from coronary thrombosis. Fifteen are alive, including 5 who received isotopes prophylactically after surgical resection of the isolated ovarian cancer; these patients are alive from 2 to 5 years after their operation and isotopic regimen. Of the additional 10 patients, 3 are living with evidence of residual cancer, one of whom is miserable because of extensive pelvic infiltration not controlled by the interstitial administration of isotopes; the other 7 are surprisingly well, with no evidence of cancer even though there was widespread cancer involving the abdominal cavity at the time of isotopic administration. The isotopes are considered to have prolonged life in this group.

An analysis of the time of death after the

isotopic regimen reveals that 20 patients died immediately or within 2 months after the therapy. There were no complications in these patients as a result of the isotopes. Rapid death after the therapeutic regimen emphasizes the fact that these patients were in terminal stages and the isotopes were administered as a last resort in the hope that something heroic might be accomplished. Failure in this respect emphasizes the futility of administering radioactive isotopes to such patients.

The average duration of life for all patients who died, including the 20 who succumbed within 2 months after isotope therapy, was 7.5 months: 17 died between the third and fifth month; 16 died between the fifth and twelfth month; 2 lived 16 months, and one 32 months after isotope therapy. One patients died 4 years after intra-abdominal isotope treatment from metastasis to the brain.

PALLIATION

An analysis of all patients treated revealed that a good result, consisting in decreased fluid formation, decrease in pain, an increased sense of well-being, and shrinkage of palpable masses, occurred in 20 patients; a fair result occurred in 22, and an equivocal result in 6; and 18 patients received no benefit. Five patients received the isotopes intra-abdominally as a prophylactic measure and the results in these cannot be evaluated; in 9 the administration was too recent for evaluation of the outcome.

As to symptomatic response: 20 patients received no benefit; 36 enjoyed a feeling of well-being; pain subsided in 35; and in 16 there was definite shrinkage of a palpable mass. Of the 16 patients who received the radioactive isotopes for the control of ascites, the control was complete in 2, partial in 12, and 12 showed no benefit. Benefit was noted in one of the 2 patients who received the isotopes for the control of hydrothorax.

No patient with evidence of intestinal obstruction benefited from the radioisotopes administered intra-abdominally. Hence, intra-abdominal isotopes are considered not indicated in the presence of severe intestinal obstruction.

The duration of palliation varied from 1 to 30 months. When symptoms recurred, a second course of isotope therapy had little effect.

The following abstracts are included as examples of techniques and the responses to isotope therapy.

Complete Control of Ascites

J. P.—39 years. Cystadenocarcinoma of ovary with peritoneal implants.
April 10, 1955. Hysterectomy and bilateral salpingo-oophorectomy.
October 1, 1956. Paracentesis: 6,000 cc. fluid with cancer cells identified in fluid.
11 mc $CrP^{32}O_4$ intra-abdominally.
August 20, 1961. No evidence of cancer.

Remarks: Complete control by a relatively small dose of $CrP^{32}O_4$ for over 6 years.

Palliation from Interstitial Isotope Therapy

F. G.—58 years. Papillary adenocarcinoma of ovary infiltrating rectum and pelvic structures.
May 16, 1957. Bilateral oophorectomy and hysterectomy: large pelvic mass residual.
May 31, 1957. Yttrium 90, 10 mc, plus 30 mg. thiotepa; mass smaller.
June 7, 1957. Yttrium 90, 30 mc; slight shrinkage of mass.
June 21, 1957. External irradiation; no benefit.
July 9, 1957. Colostomy.
September 19, 1957. Yttrium 90, 40 mc; mass smaller.
November 4, 1957. Iridium seeds, 40 mc; slight superficial necrosis.
April 24, 1958. Yttrium 90, 25 mc, plus 30 radon seeds, 1.5 mc each; no significant change.
June 18, 1958. Yttrium filament, 17,000 eq. β roentgen per linear cm. at 0.5 cm. distance.
October 25, 1958. Patient expired.

Remarks: This case illustrates partial control of a pelvic cancer that obstructed the rectum, treated by repeated injections of radioactive isotopes interstitially into the cancer by way of the vagina. Most of these

were performed as office procedures. They produced a minimum of trauma to the patient, a factor which must be considered in a palliative program. The patient enjoyed a relatively comfortable existence for 1.5 years as the result of interstitial isotope therapy.

The efficacy of this regimen in certain instances is evidenced by a 6 year "cure" of a huge primary malignant melanoma of the vagina by interstitial radioactive isotope therapy.[3]

Isotope Treatment of Hepatic Metastases

L. T.—51 years.

December, 1954. Bilateral salpingo-oophorectomy for bilateral cystadenocarcinoma (low grade). (Hysterectomy previously for fibroids.)

October, 1956. Metastases to lungs, bilateral cervical lymph nodes, and liver; roentgen therapy to cervical lymph nodes and lung; moderate regression.

October, 1957. Ascites and enlarged liver; 4 mc $CrP^{32}O_4$ into hepatic artery; 10 mc yttrium 90 into hepatic mass.

December, 1957. Patient expired.

Remarks: This case demonstrates an effort to control metastasis to the liver by means of radioactive isotopes. The patient had extensive cancer involving most of the abdomen and the liver, as well as bilateral metastases to the cervical lymph nodes and the lungs. The pulmonary and lymph node metastases were treated by external irradiation. The hepatic metastasis was treated by radioactive isotopes. One course of isotopes was injected directly into the hepatic artery via a percutaneous route in a catheter in the femoral artery, which was then threaded through the aorta to the level of celiac axis. Placement of the Geiger Müller counter over the liver showed a marked uptake of the isotope by the liver, including the neoplasm. Inasmuch as the tumor is supplied by blood from branches of the hepatic artery, the preferable way of administering any agent, either chemotherapeutic or isotopic, is via the hepatic artery. In addition to the intra-arterial therapy, the patient received radioactive isotopes delivered interstitially by the percutaneous route, under scintiscanning direction of radioactive yttrium, directly into the liver. There was marked shrinkage of the hepatic mass, with relief to the patient from pressure by this enlarged mass. The treatment was not considered to have any effect on the over-all course of the disease, and the patient rapidly developed extension of the cancer and died only 2 months after the institution of therapy.

An interesting feature of this case is that, despite histologic evidence of a neoplasm of very low-grade malignancy, the patient died 3 years after the initial operation from widespread dissemination of her cancer.

Control of Pleural Effusion in a Patient with Extensive Dissemination of Ovarian Cancer

N. S.—52 years. Papillary cystadenocarcinoma, metastatic to abdomen, liver and chest; bilateral pleural effusion.

September, 1955. Exploratory laparotomy.

December, 1955. $CrP^{32}O_4$, 15 mc, and 40 mg. thiotepa into right chest cavity after thoracentesis; 10 mc $CrP^{32}O_4$ into abdominal cavity after paracentesis; deep roentgen therapy, 2,400 r to each of two portals of right hypochondrium; control of right hydrothorax and ascites.

April, 1956. Roentgen therapy to mass in pelvis; 15 mc $CrP^{32}O_4$ into left chest for massive left pleural effusion causing severe dyspnea; pancytopenia.

July 28, 1956. Patient expired; no further effusion into pleural space.

Remarks: This case demonstrates the role of radioactive isotopes in the over-all control of a patient with disseminated ovarian cancer. The large masses involving the pelvis were treated by external irradiation inasmuch as the radioisotopes, because of their lack of penetration, would not be expected to affect these. The patient's ascites was treated by radioactive isotopes, but the main function here was the control of pleural effusions. A right pleural effusion was completely controlled for approximately 8 months by combined isotope and chemotherapy, and an extensive left pleural

effusion which caused severe dyspnea was controlled for 4 months, at which time the patient expired.

Prolonged Palliation by Combined Isotope Therapy

E. K.—Papillary cystadenocarcinoma; extensive abdominal metastases, large pelvic mass.
September 25, 1958. Y^{90}, 50 mc intra-arterially.
January 28, 1959. Au^{198}, 20 mc direct into abdomen.
September 15, 1959. Co^{60} vaginal applicator; 2,079 mg. hr. radium equivalent.
July 7, 1960. $CrP^{32}O_4$, 15 mc direct into abdomen.
October 28, 1960. $CrP^{32}O_4$, 10 mc direct into abdomen.
March 10, 1961. $CrP^{32}O_4$, 30 mc interstitially into pelvic mass.
March 14, 1961. Silver-coated gold, 25 mc interstitially into pelvic mass.
May, 1961. Patient expired.

Remarks: This patient enjoyed a comfortable period of 2 years and 8 months from combined isotope therapy.

Intra-abdominal Isotopes, Subsequent Pregnancy, and Intra-abdominal Isotope Therapy during Pregnancy[2]

C. L.—22 years. Papillary cystadenocarcinoma of both ovaries with extensive intraperitoneal implants; omentum solid with cancer.
July, 1959. Right oophorectomy and appendectomy.
August 4, 1959. $CrP^{32}O_4$, 20 mc, plus Au^{198}, 75 mc, intra-abdominally.
February 27, 1960. $CrP^{32}O_4$, 20 mc, intra-abdominally.
June 16, 1960. Five month fetus noted.
September 18, 1960. Normal baby delivered by cesarean section.
May 10, 1962. Mother and baby doing well.

Remarks: The second course of isotopes (February 27, 1960) was given when the patient was 1 month pregnant. The child is normal, with no evidence of her intrauterine radioactive environment 18 months later.

It is estimated that the patient received approximately 100,000 rads from the combined isotope therapy to the abdominal cavity.

COMPLICATIONS

No patient suffered any serious complication; *i.e.*, perforation of bowel, infiltration of a solid viscus, etc. from the isotope administration. Three patients suffered from infiltration of isotopes in the abdominal wall, and in 2 there was seepage of isotope-containing fluid from the abdominal cavity after the administration of the isotopes; this caused an erythematous reaction about the puncture wound where the isotopes were administered. In both instances, the reaction subsided spontaneously in 5 to 10 days. In the third patient, the reaction persisted for 3 months.

Two patients developed severe paralytic ileus, with marked intestinal distention, after the administration of the isotopes. It is believed that the isotopes produced a form of chemical peritonitis, resulting in ileus. In both instances, the ileus subsided after medical management with no severe residuum. This phenomenon was also observed by Rose.[16] One patient had severe pain at the site of injection of the radioactive isotopes; the pain was intra-abdominal, and it is interpreted that the material may have been injected directly into the omentum causing the painful reaction.

Hematopoietic depression was not observed in any patient who received radioactive isotopes as the exclusive therapy. Three patients suffered from pancytopenia; 2 of these had received chemotherapy previous to the isotope regimen. All blood elements participated in the drop but rose rapidly after the administration of 1,000 cc. of fresh whole blood. The third patient suffered a fatal aplasia from combined external irradiation, chemotherapy and isotope administration.

DISCUSSION

Large doses of superficial irradiation can be given by the intra-abdominal administration of radioactive isotopes. The poor cure rate for ovarian cancer, averaging about 30 per cent 5 year cures, emphasizes the need for improved treatment methods. Many recurrences of ovarian cancer are

probably due to the rupture of cysts containing fluid in which float cancer cells that produce deposits of cancer throughout the peritoneum. Such seeding produces a situation that is ideal for treatment by the intra-abdominal administration of radioactive isotopes. The fact that 5 patients treated by postoperative isotope administration are doing well from 2 to 5 years after excision of their ovarian cancers suggests that the isotopes were beneficial in helping to control possible growth from seedings. This is speculative, and one cannot make a definite statement as to the effects of the isotopes in controlling recurrences in these 5 patients.

Greenberg and Dudley[11] have reported 11 patients who received Y^{90} prophylactically after intraperitoneal spillage of cancer during surgical manipulation, and 7 patients with extension of ovarian cancer who received Y^{90} intra-abdominally; 15 are alive and well, 6 for more than 5 years. Rose[16] reported 24 patients treated prophylactically postoperatively because of ruptured cystadenocarcinoma; 18 (75 per cent) are alive and well from 6 to 76 months after treatment. Two of the group are alive without evidence of tumor; 4 have died of their cancer, and 2 are alive with recurrent cancer. Six of the group later developed intra-abdominal cancer.

The fact that approximately 75 per cent of the patients develop postoperative intra-abdominal cancer, which often starts as tiny growths resulting from the adherence of cancer cells to visceral and parietal peritoneum, strongly suggests that isotope administration is indicated prophylactically after the excision of ovarian cancers. Five year and ten year follow-up of larger series of cases will be necessary to determine the absolute value of this regimen.

The observation that one patient (C. L.), who had extensive intra-abdominal metastases including an omentum solid with cancer, was apparently cured for 2.5 years by the intra-abdominal administration of isotopes, even to the point of delivering a normal baby, indicates the efficacy of intra-abdominal isotopes in controlling some cancers.[2]

Cancer seedings are an important factor in the production of fluid, and the intra-abdominal administration of isotopes is an ideal means of destroying the cancer cells and controlling intra-abdominal fluid. Other studies in this clinic have demonstrated that fluid accumulates in the abdomen owing to peritoneal cancer seedings or obstruction to circulation. It has been the author's policy that, if a patient does not respond to the intra-abdominal administration of isotopes on two occasions, further isotope therapy be abandoned and reliance placed on irradiating by external means the region of the porta hepatis. Evidence has accumulated demonstrating that ascites occurs as the result of circulatory compromise in the region of the porta hepatis and that irradiation from external sources to this region is beneficial in controlling the ascites.

Certain patients may have large masses involving the abdomen as well as seedings. Intra-abdominal isotope administration will control the smaller tumefactions scattered throughout the abdomen but will have little, if any, effect upon the large masses because of the superficial nature of the irradiation. Accordingly, it is our policy to administer intra-abdominal radioactive isotopes for the control of the seedings and depend upon external irradiation, given over more limited ports, to aid in the control of larger masses.

When patients have pelvic deposits, palliation can often be obtained by the judicious use of isotopes injected interstitially into these pelvic tissues. This has been done in a number of patients whose masses were observed to be inoperable, and who received interstitial isotope irradiation at the time of operation, or postoperatively via the intravaginal route. The procedure is atraumatic, is not time-consuming, and is often effective. It is realized that the dose of radiation given by this technique usually lacks homogeneity, but excellent palliation can frequently be obtained. Experiments

are in progress to improve the logistics of administration of isotopes interstitially to assure a more homogeneous dose. The intra-abdominal administration of radioactive isotopes has been combined with the interstitial administration of isotopes delivered per vaginam, with pelvic irradiation from a Co^{60} intravaginal applicator designed by the author, or with teletherapy.

The observation that omental masses disappeared after isotope therapy in some patients suggests that the omentum, which is known to concentrate cancer cells as part of its function of being a "catch-all," also concentrates colloidal radioisotopes administered intra-abdominally, making this an effective measure for destroying cancer within the omentum.

An autopsy on one patient who had had extensive generalized carcinoma revealed only a few scattered foci of cancer cells within a dense fibrous mesh. In 2 patients on whom exploratory operations were performed months after intra-abdominal isotope therapy, only a large pelvic mass was found in each instance, whereas previously they had had generalized intra-abdominal metastases.

Rose[16] reported one patient who died from malignant hypertension 72 months after Au^{198} therapy for widespread peritoneal seedings in the abdomen and pelvis and in whom no trace of cancer was found on postmortem examination.

The relative benefits of one isotope over another, and the question of whether giving combined isotopes, as practiced by the author, is more beneficial require further investigation.

Experience with the administration of radioactive isotopes intravascularly into the abdominal aorta as a means of delivering them via the arteries to the tumors is too meager to warrant any conclusion. The results have not been spectacular and continued efforts in this direction are planned. Ceramic microspheres, 60 microns in diameter and tagged with Y^{90}, are being used in this investigation.

Patients with intestinal obstruction have not benefited from radioactive isotopes, suggesting that their administration is not indicated in such cases. Furthermore, patients in a severely debilitated state, with far-advanced cancers, have in no way benefited, indicating that radioactive isotopes are also contraindicated in such instances.

The recent report of Santoro, Griffen, and Wagensteen[18] on the second-look operation at varying times after the original operation, for the surgical excision of recurrences, will contribute to our knowledge of the natural history of ovarian cancer, but it is doubtful if the procedure will find wide clinical application.

The question of the administration of cancer chemotherapeutic drugs in preference to, or simultaneously with, other modalities including radioactive isotopes is being investigated. It has been my experience that all drugs presently available, with the exception of methotrexate given for choriocarcinoma, exert but a transient effect. I have given them concurrently with radioactive isotopes but always cautiously, because the drug is absorbed and may exert an adverse effect upon the hematopoietic system. The data will be reported later.

CONCLUSIONS

1. The intra-abdominal administration of certain radioactive isotopes is effective in destroying intraperitoneal ovarian cancer seedings and small omental cancer masses.

2. Its use appears indicated prophylactically after operation for ovarian cancer. Further studies are needed to confirm this impression.

3. Ascites due to ovarian cancer was completely controlled in 5 per cent of patients, partially controlled in 47 per cent, and unaffected in 47 per cent after intra-abdominal administration of radioactive isotopes.

4. Combined radioactive isotopes—one with a short half-life (Au^{198}, Y^{90}) and one with a long half-life ($CrP^{32}O_4$)—were used. This combination is believed preferable to injecting a single isotope, but additional studies are being made to confirm this

preliminary impression.

5. Intra-abdominal radioactive isotopes combined with teletherapy is a useful means of treating small and larger-sized deposits of ovarian cancer.

6. The interstitial administration of radioactive isotopes is a useful means of irradiating pelvic cancer.

7. One patient is apparently cured and delivered a normal baby 2.5 years after the intra-abdominal administration of radioisotopes.

8. The average duration of life after radioisotope therapy of the 58 patients who have died was 7.5 months. It is believed that life was significantly prolonged in 10 patients.

9. Palliation (a sense of well-being, shrinkage of masses, decrease in fluid accumulation, and decrease in pain) occurred in approximately 50 per cent of the patients. Palliation was considered good in 25 per cent, fair in 25 per cent, equivocal in 8 per cent. No benefit was observed in 20 per cent of the patients.

10. The complications of radioactive isotope therapy are minimal.

11. Patients with intestinal obstruction and those severely debilitated respond poorly, and radioactive isotope administration is contraindicated in such instances.

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THE INCIDENCE AND APPEARANCE OF ROENTGENOLOGICALLY VISIBLE PSAMMOMATOUS CALCIFICATION OF PAPILLARY CYSTADENOCARCINOMA OF THE OVARIES

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THE striking roentgenographic features noted in a recent case of psammomatous metastatic calcifications in a young female with papillary cystadenocarcinoma of the ovary prompted the authors to review the literature on this subject and present what appears to be one of the most remarkable cases of this entity reported.

Serous cystadenomata are one of the most common of ovarian tumors, various authors having related their incidence at from 15 to 33 per cent[2,3] of cystic tumors of the ovaries. They may occur in any age group although usually from the age of 30 to 60 and are thought to arise from the germinal epithelium of the ovary.[10]

These tumors may be simple cysts or have papillary excrescences within them. The presence of such papillary projections increases the malignant potential and, indeed, papillary serous cystadenocarcinomata are probably the most common malignant ovarian lesions.

Kent and McKay[5] in their analysis of 2,530 cases of ovarian tumors report that 24.5 per cent of these were serous cystadenomata with a malignancy rate of 34.5 per cent. Thus, of 349 malignant ovarian tumors, 214 (the most abundant) were serous cystadenocarcinomata. On sheer numerical grounds alone, not to consider the morbidity and mortality, these are important lesions.

Calcification within these tumors may be a prominent feature both of the primary and metastatic areas.[6] Microscopically, this most often occurs in the form of discrete entities known as corpora amylacea or psammoma bodies. The histologic appearance of these tumors including the psammoma bodies has been well described in standard texts. A photomicrograph is included chiefly to show the abundant calcification present throughout the tumor (Fig. 1).

This calcification may be discernible on roentgenograms in a distinctive fashion both in the primary and metastatic lesions. Previous reports have been made, one of the earliest being Loud's[7] in 1936. These reports have been scanty in recent years and none has cited the incidence wherein these lesions might be roentgenologically discernible. With this in mind, we have reviewed the records of the past $3\frac{1}{2}$ years at the U. S. Naval Hospital, San Diego, and will summarize these data, presenting 4 cases in detail including the one referred to in the opening paragraph.

CLINICAL MATERIAL

Forty-three cases coded under the Armed Forces Pathologic Nomenclature as Cystadenocarcinoma (#1430), Adenocarcinoma (#1400) or Carcinoma, n.e.c. (#1490) primary in ovary were reviewed from the Clinical Index of the U. S. Naval Hospital, San Diego, covering a period from 1957 to 1961. The results of histologic examination at either necropsy or of surgical specimens revealed 34 of these to be papillary cystadenocarcinomata. Roentgenograms were available and reviewed carefully on 33 of these patients. Four of the 33 patients were thought to have roentgenographic evidence of calcified tumor in metastases. Psam-

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The opinions or assertions contained in this article are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department, or the Naval Service at large.

moma bodies were noted in abundance on review of the slides.

Microscopic evidence of calcification in the form of psammoma bodies was reported on 7 other patients with this disease. None of these patients revealed definite roentgenographic evidence of psammomatous calcification however. Presumably this was due to lack of sufficient amount of psammoma bodies within the tumors. In our 4 reported cases the correlation between the microscopic abundance and the roentgenographic prominence of the psammomatous calcification was excellent and in direct proportion as may be expected. The over-all incidence of roentgenologically discernible calcification in the 33 cases of papillary cystadenocarcinoma was therefore 12 per cent. This was somewhat higher than we expected and reflects, we believe, closer application of the findings elucidated in this paper.

REPORT OF CASES

Case I. L.J., a 31 year old white female, was admitted to the U. S. Naval Hospital, San Diego on May 26, 1960 with the chief complaint of severe vomiting. Her past history revealed a right salpingo-ovariectomy in 1950 for a reportedly benign cyst. On July 18, 1956 a total hysterectomy and left salpingo-ovariectomy and appendectomy were done for an adenocarcinoma of the left ovary. Orthovoltage roentgen therapy was given to a total of 1,800 rads to each of two ports, anterior and posterior over the pelvis. The patient did well for approximately 2 years when she developed signs of intestinal obstruction which progressed until 1959 at which time a laparotomy was performed wherein peritoneal, omental and serosal metastases were noted. A colostomy was done. The pathologic diagnosis was metastatic papillary cystadenocarcinomatosis, primary in ovary.

She again did well until April of 1960 at which time she was admitted to our hospital. Roentgenograms at this time revealed advanced metastatic calcified densities throughout the abdomen. A metastatic lesion in the anterior chest was also present. The pelvis was completely filled with calcified tumor (Fig. 2, 3 and 4). A second laparotomy was required to alleviate recurrent bowel obstruction. Two of the largest masses in the pelvis were removed, one of which was completely encircling the sigmoid colon (Fig. 5 and 6). The gross tumor had a sandy consistency to palpation and was quite gritty to section. Innumerable psammoma bodies were present on microscopic examination (Fig. 1). The patient did fairly well only for a short period and re-entered the hospital with vaginal bleeding of sufficient amount to require repeated transfusions. It was decided that an attempt at further radiation therapy might be valuable. The patient then suddenly also developed a small bowel vaginal fistula. Cobalt therapy was continued with moderate success in that the bleeding stopped and the amount of fecal discharge decreased.

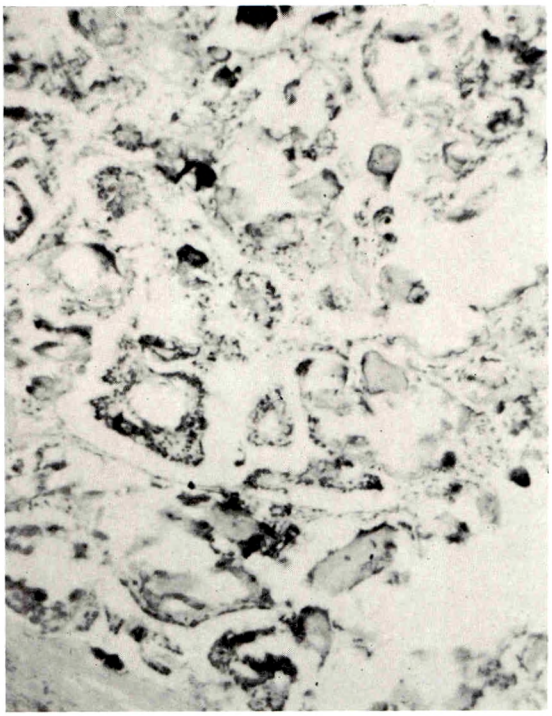


Fig. 1. Case I. Photomicrograph showing the abundant calcification present within the tumor (darker staining areas, H. & E.).

Over the last few months the patient has grown steadily weaker and is now terminal.

Case II. M.P., a 54 year old white female, was examined in January, 1961, with a chief complaint of pressure in the vagina and rectum associated with dyspareunia. Her last menstrual period had been in 1952.

Examination revealed a 10 by 12 cm. mass which was firm and situated in the midline. Rectovaginal examination suggested an exten-

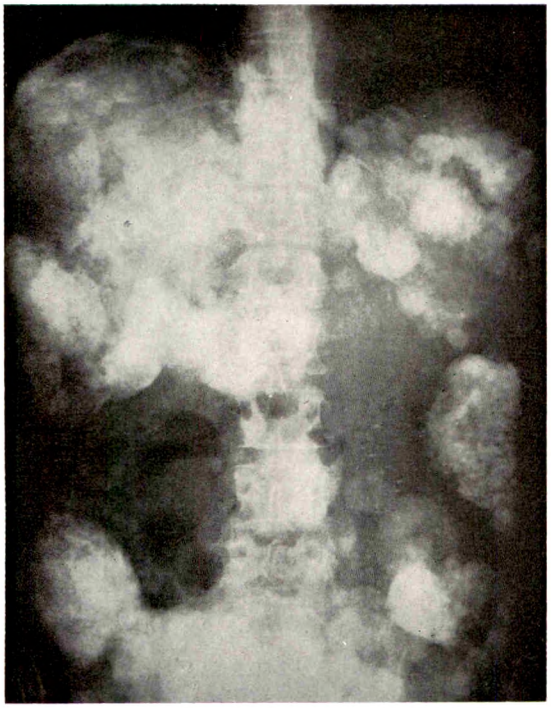


FIG. 2. Case 1. Diffuse psammomatous metastasis. Note that many areas suggest that there is barium within the colon and small bowel. Several competent observers without benefit of history were consequently led to believe that this study represented barium within the abdominal cavity secondary to a ruptured bowel during examination.

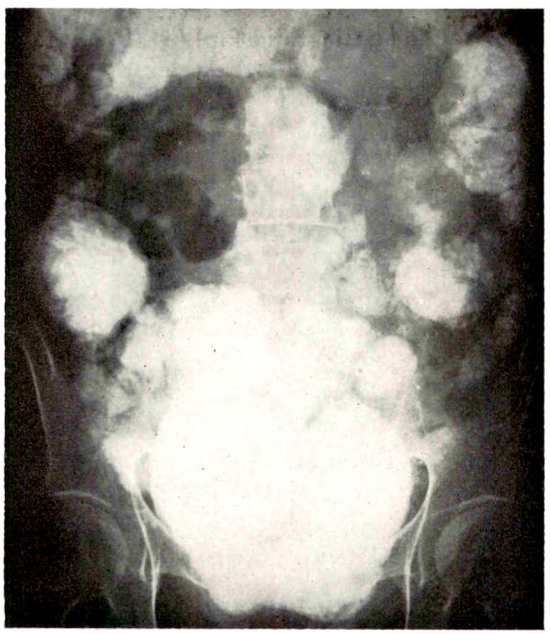


FIG. 3. Case 1. Roentgenogram of lower abdomen showing identical findings. The psammomatous calcifications fill the entire pelvis and appear to have deposited over multiple areas of the serosa of the bowel.

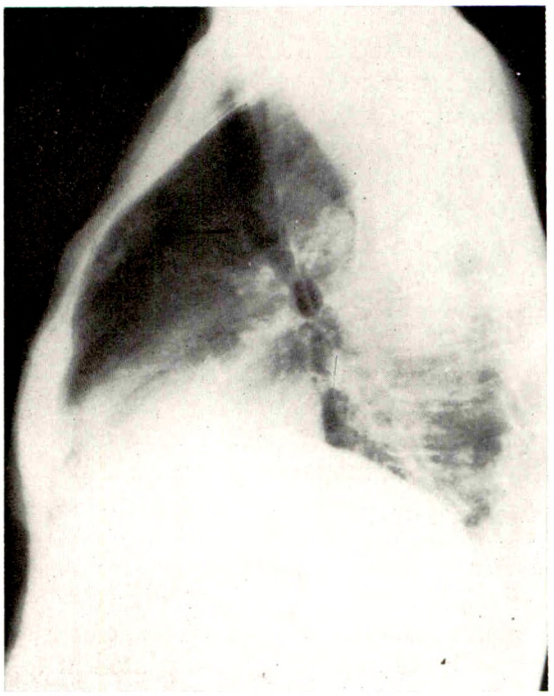


FIG. 4. Case 1. Calcified metastatic lesion to anterior chest wall, probably subpleural (arrow). This is a rare finding in this disease.

sion of this mass posteriorly into the cul-de-sac. The uterus was thought to be normal.

Laparotomy revealed massive metastatic lesions to the peritoneum, omentum and bladder surface. The right ovary was three times its normal size and completely replaced with tumor. Deposits were noted on the serosa, on the sigmoid, rectosigmoid and transverse colon. Both ovaries were removed but further surgery was not deemed advisable. Pathologic examination revealed typical papillary cystadenocarcinoma with prominent psammoma bodies throughout the lesions. She subsequently received cobalt therapy and has done well to date.

During a review of this patient's roentgenograms, a fine granular appearing density was noted in the right lower quadrant. Examination of numerous films revealed this to be unchanged over a period of several months. Apparently this had been interpreted as feces within the

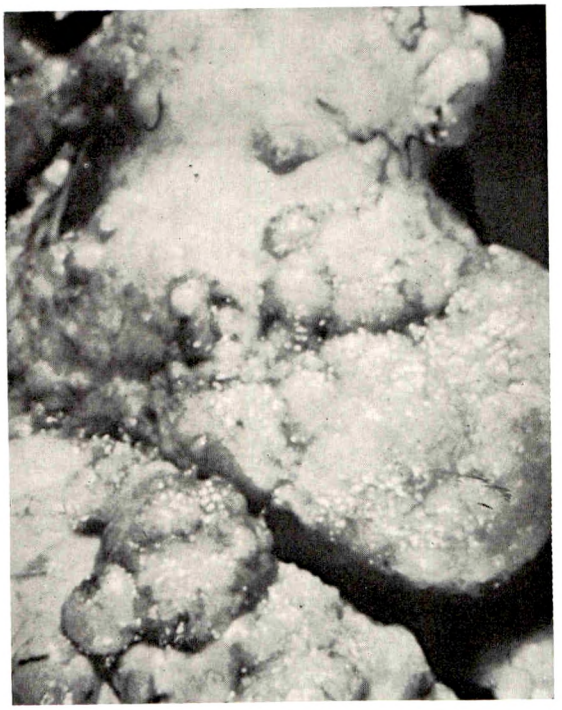


Fig. 5. Case I. Surgical specimen removed from pelvis.

colon although close scrutiny suggested that the density extended beyond the bowel lumen. This finding was thought to be representative of faintly appearing, but nevertheless definite, psammomatous calcification (Fig. 7).

Case III. C.Y., a 55 year old female, had a cystadenocarcinoma of the right ovary removed surgically in 1955. A calcified mass was reported as being visible on abdominal roentgenograms at that time. Peritoneal and serosal implants were noted at surgery. A right ovarian cystic lesion was removed and this was followed by radioactive gold treatment.



Fig. 6. Case I. Roentgenogram of surgically removed tumor. The fine granular calcifications which pervade the tumor are now clearly seen.

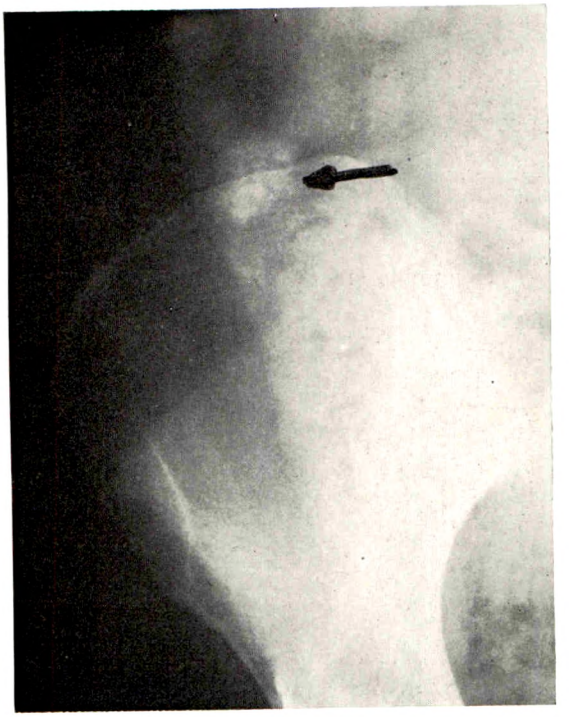


Fig. 7. Case II. The psammomatous densities (arrow) persisted over a long span of time eliminating the possibility that they represented impacted fecal matter.

Subsequent recurrence in 1957 was noted with development of abdominal masses and skin nodules. Cobalt radiation therapy, nitrogen mustard therapy and cytoxan were used over the next 4 years with good palliative relief. The patient expired in 1961 and large, multiple, intra-abdominal masses and metastatic serosal and peritoneal implants were noted at necropsy. Histologic examination revealed papillary cystadenocarcinoma with psammomatous calcification within the metastatic tumor nodules.

A review of the roentgenograms disclosed fine granular appearing densities within the abdomen which had been taken for feces in the colon. Careful evaluation revealed these to be unchanging in appearance and to extend beyond the bowel wall in a fashion consistent with psammomatous calcification of the tumor (Fig. 8).

Case IV. P.K., a 61 year old white female, was admitted to the U. S. Naval Hospital in June of 1961 with a palpable pelvic mass associated with lower abdominal pain and tenderness. No vaginal bleeding was noted however.

Exploratory laparotomy revealed a large left

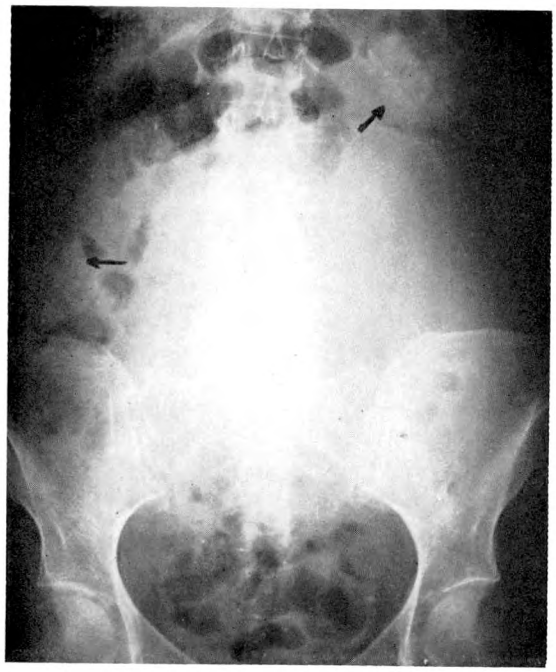


FIG. 8. Case III. Faint granular densities (arrows) thought initially to be feces. Note that the calcifications extend beyond the bowel wall. The large central tumor mass was for the greater part cystic in nature but did contain diffuse psammoma bodies which may have increased its opacity.

ovarian cyst with extensive metastatic carcinomatosis involving the pelvis, omentum, liver and bowel serosal surfaces. Microscopic examination showed papillary cystadenocarcinoma with psammomatous calcification.

A left salpingo-ovariectomy was done and was followed by cobalt irradiation to the abdomen. Mottled fine calcification was also noted in the right lower pelvis in the area of metastatic disease which was thought to be consistent with psammomatous calcification (Fig. 9).

The patient has done well following therapy.

DISCUSSION

Previous authors[4,6–8] have characterized the calcium visible within these tumors as fine, granular and of less density than any of the other common calcific lesions in the abdomen. The rather extensive distribution throughout the abdomen has also been stressed.[6] Our series of cases again revealed this to be true. We, however, wish to emphasize the resemblance to ingested barium of several days duration and to point out the tendency of metastatic serosal implants to outline the bowel, as noted in Case I. The combination of these characteristics, especially the serosal implants, may be a source of error to both the clinician and the radiologist[1] and often leads to the mistaken conclusion of previously ingested or inserted barium and/or feces in the bowel. Cases III and IV tend to illustrate this.

It is felt that remembrance of the above will result in clearer appreciation of the appearance of psammomatous calcification and more instances of roentgenologic diagnosis of it.

Since none of the previous reports had attempted to relate the incidence of roentgenographically visible psammomatous calcification, we surveyed our records with this as a secondary purpose. The incidence of 12 per cent is felt to be higher than expected and reflects closer and more careful inter-

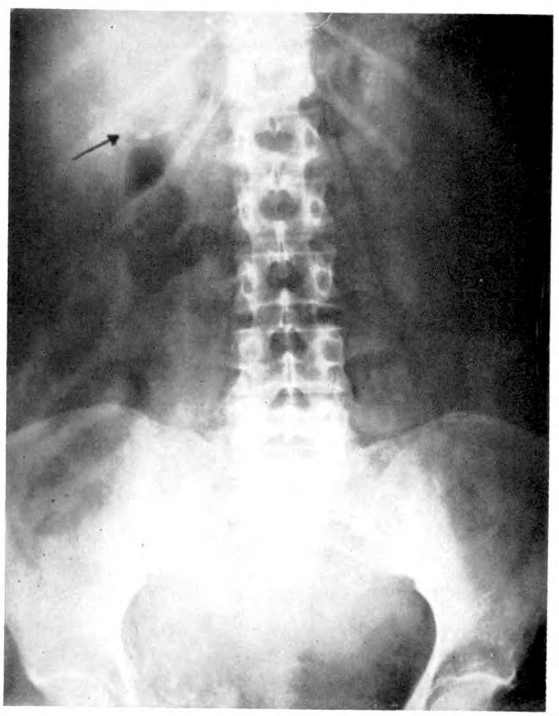


FIG. 9. Case IV. The calcification in the right upper quadrant of the abdomen (arrow) is biliary. The mottled calcifications in the right lower quadrant correspond to metastatic tumor deposits.

pretation in light of the above described characteristics.

It may be stated finally that the visibility of the calcium on roentgenograms varies directly with the amount present microscopically although, of course, the extent of metastasis is not similarly related.

SUMMARY

1. Four cases of papillary adenocarcinoma primary in the ovary are presented with roentgenographic evidence of calcification within psammoma bodies common to these tumors.

2. A review of the records at the U. S. Naval Hospital, San Diego, reveals an approximate incidence of 12 per cent of our cases to have had roentgenographically visible psammomatous calcification.

3. A brief discussion of the appearance of these calcifications is added with attention to their resemblance to ingested barium and/or feces. The frequency with which serosal implants outline the bowel is stressed.

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CHRONIC LYMPHOCYTIC LEUKEMIA AND RADIATION THERAPY*

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CHRONIC lymphocytic leukemia is characterized by both prognostic and cytologic factors. The expected duration of life is from 1 to 20 years or more, the average being 3 to 5 years after the onset of the first symptoms.[6] Cytologically, there is a peripheral mature lymphocytosis with an associated proliferation of lymphoid cells throughout the blood forming organs. This feature differentiates it from lymphosarcoma which may have the same tissue changes,[2] and from Hodgkin's disease which may have a leukemic blood picture.[12]

For nearly 60 years, chronic lymphocytic leukemia has been treated with radiation therapy.[27,34] Roentgen rays have been applied regionally, usually to the spleen or enlarged lymph nodes,[3] or to the total body[24] in either intensive short courses or prolonged periods of low dose administration. Radiation has also been delivered internally with radioactive phosphorus (P^{32}).[17] Furthermore, beginning with the introduction of methyl-bis (B-chloroethyl) amine hydrochloride (nitrogen mustard) in 1946,[13] about 30 different alkylating agents of the nitrogen mustard type have been clinically studied.[32] The partially successful ones have included methyl-bis (B-chloroethyl) amine hydrochloride; triethylene thiophosphoramide (Thio-Tepa, TSPA);[36,38] triethylene melamine (TEM),[30,31,41] used in 1950 as the first mustard derivative for oral administration; myleran, a derivative with a different alkylating side chain; and chlorambucil (CB 1348) or leukeran, the most effective and introduced by Galton and associates in 1955.[11] Corticosteroids have been tried as specific antileukemic agents, but the results have been unsatisfactory and they should be reserved for complicating hemolytic anemia and/or thrombocytopenia.[35]

MATERIAL

A series of patients with chronic lymphocytic leukemia treated solely with roentgen rays at Harper Hospital, Detroit, Michigan, during the past 38 years is presented. The patients are classified according to sex and age. The long term results of treatment are compared with several series from the literature in which some type of radiation therapy had been utilized as the predominant method. An attempt is also made to compare the patient response when some of the newer chemotherapeutic agents were used as reported in the literature with that obtained by regional external radiation therapy.

From 1922 through December, 1960, 150 patients with active chronic lymphocytic leukemia have received regional external roentgen therapy as their primary treatment. Of these, there were 33 who died, or were lost to follow-up and were presumed to have died, within 3 months of the initial dose of radiation; it is felt that they received an inadequate trial of treatment. The survival dates are calculated from the time the patient received his initial treatment to the time of death, or until the patient was lost to follow-up. Patients lost to follow-up have been included and such patients are presumed dead.

Prior to the use of alkylating or so-called radiomimetic drugs, radiation therapy proved to be of much greater value than the use of arsenicals or any other treatment method. Therefore, the results obtained with radiation therapy could also be used for estimation of the value of various chemotherapeutic agents. A statistical analysis of our cases with an explanation of the method of treatment is presented as a yardstick by which a comparison can be

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made with the newer chemotherapeutic methods.

SEX INCIDENCE

Ninety-six of the patients in our series, or 64 per cent, were males and 54, or 36 per cent, were females. This is a ratio of 1.7:1 of males to females. In a review of six reported large series[4,6,22,26,33,37] since 1924, it is interesting to note that there has been progressive increase in the percentage of cases of chronic leukemia in females as compared to males. In the earliest of those series reported in 1924,[22] 26 per cent of the cases were females as compared to 36 per cent in the present series. Prior to 1940 in our group of cases there were 25 males and 10 females, a ratio of 2.5:1. Since 1940, 71 were males and 44 were females, a ratio of 1.6:1.

AGE DISTRIBUTION

The patients' ages ranged from 32 years for the youngest to 91 years for the oldest when seen at the time of their initial treatment. The average age of the females was 58.4 years and of the males 56 years, or a general average of 56.7 years. These findings are comparable with those of other series[6,22,25,26,28,33] and demonstrate again that chronic lymphocytic leukemia is a disease of elderly patients, occurring most commonly after the fifth decade of life.[14]

METHOD OF TREATMENT

In all of our cases, roentgen therapy was the only specific method used. Patients in this series for whom treatment had been prescribed or given are those in whom the disease was active or causing symptoms. In those patients where the diagnosis of chronic lymphocytic leukemia was made, but in whom an abnormal blood picture was the only finding, treatment was delayed until there was evidence of progression of the disease or decrease of the normal efficiency. This might be manifested by an increase in lymphocytosis, development of anemia, a decrease in the number of platelets or increased debility. Development of hepatosplenomegaly and enlargement of the lymph nodes were also felt to be an indication for therapy.

Following its introduction in 1946, nitrogen mustard therapy was given a trial in a few patients. Although we believe nitrogen mustard to be of value in the treatment of Hodgkin's disease[7] and some types of carcinoma of the lung,[16] it was found to be of little benefit in the treatment of chronic lymphocytic leukemia; therefore, roentgen therapy has been continued in these cases. Supportive treatment, such as antibiotics to control infection and blood transfusions to correct anemia, was given when indicated. Corticosteroids also have been used as ancillary medication in the last few years, mostly in the latter stages of the disease. Although supervoltage therapy has been available at Harper Hospital since 1932, we have found the lymphocytic cells to be so radiosensitive and the dosage level needed so small that we have consistently employed conventional therapy.

During the early years 200 kv. peak with 1 mm. Cu filtration, corresponding to a half-value layer of 1 mm. Cu, was used. More recently, and at present, 225–250 kv. constant potential with Thoraeus filtration, corresponding to a half-value layer of 3 mm. Cu, is employed.

Before radiation therapy is undertaken, a clinical and laboratory appraisal of the patient is made. If there is no peripheral lymphadenopathy, only a large area over the left upper anterior abdomen to include the spleen and retroperitoneal lymph nodes is treated, usually with a dose of 200 r in air at triweekly intervals. If lymphadenopathy is present, the enlarged lymph nodes are irradiated weekly and then at gradually spaced intervals with 150 to 200 r in air. The total dose is not predetermined but usually a dose of 150 to 1,000 r is given, depending on the radiation response of the patient which varies from case to case. Concomitant irradiation of the spleen is carried out as it is thought that this increases the radiosensitivity of the super-

ficial lymph nodes and prevents recurrence in irradiated areas.[20] An explanation is that the breakdown products of the irradiated splenic tissue which are discharged into the circulation depress the activity in the lymph nodes. This theory is based on the "alarm reaction" of Selye.[23]

The patient's general condition and the laboratory data are closely watched and the intervals of treatment are lengthened, or rarely, shortened, to preserve a satisfactory clinical and symptomatic state. Although leukocytosis in itself, unless very high, is not considered an indication for therapy, once irradiation is instituted it is usually continued at regular intervals until the white blood cell count is below 30,000 per cu. mm. and may be protracted for years. Treatment may also be given in the presence of a lower white blood cell count if large tumor masses are noted that cause symptoms or are otherwise distressing to the patient. Treatment is directed to the lymph node masses or to the spleen.

DOSAGE IN RELATION TO SURVIVAL

Table I shows a summary of the treatments given, as described above, to patients surviving 3, 5, 10 and 15 years. As part of the nature of this disease there are, even in greater degree than with other lymphomata, variations from patient to patient in the activity of its progress. Those patients showing the greatest activity received the greatest number of treatments and also had the poorest prognosis. This is well illustrated in Table I. The patients surviving 3 years needed an average of 1,334 r in air per year for any single patient, while those surviving for a longer time interval needed decreasing amounts in relation to survival time. Those patients surviving for 15 years needed an average of only 231.1 r in air per year. Obviously, also the length of remission and the interval between treatments were longer in those individuals with a more chronic form of the disease or in those whose natural resistance to lymphocytic leukemia was high.

TABLE I

AMOUNT OF NECESSARY TREATMENT RELATED TO SURVIVAL TIME

Survival Time (yr.)	No. of Patients	Average Total Treatments Per Patient	Average r in Air Per Patient	
			Total	Per Year
3	58	20.2	4,002	1,334
5	34	23	4,539	908
10	10	26	4,471	447.1
15	3	28	3,466.6	231.1

RESULTS

Table II gives the absolute long term survival rates of the patients who had an adequate therapeutic trial. Patients who died or were lost to follow-up within 3 months of initial treatment are excluded. Of the remaining 117 patients 91, or 77.7 per cent, survived 1 year; 34, or 30.3 per cent, survived 5 years; 10, or 12 per cent, survived 10 years, and 3, or 5 per cent, survived 15 years.

Prior to 1940, of the 27 patients treated 22.2 per cent survived 5 years. Since that time 85 additional patients have become available for 5 year survival appraisal with an over-all average of 30.3 per cent. This might suggest that patients are either coming earlier for treatment, or that by clinical experience the treatments are more efficacious. More likely, however, this increase is due to better supportive care which includes better control of infection by the use of antibiotics and better management of transfusions. These two factors, with generally improved medical care, are probably

TABLE II

ABSOLUTE SURVIVAL PERCENTAGES AFTER INITIAL TREATMENT 1922–1960

Survival Years	Total No. of Cases	No. of Survivals	Per Cent
15	59	3	5
10	83	10	12
5	112	34	30.3
1	117	91	77.7

enough to account for the better survival figures.

A comparison of our results with those of other investigators reporting long term follow-up studies is presented in Table III. A statistical compilation of the results of therapy is only valid when the groups compared have (1) approximately the same degree of involvement before therapy, (2) comparable ancillary care, and (3) the same method of follow-up and calculation of survival rates. Bethell[4] stated that the clinician who treats every case of chronic lymphocytic leukemia when first seen with a particular form of radiation or a non-alkylating agent will report much better results than his colleagues who withhold therapy in cases which do not appear to be progressive.

Our series included only symptomatic patients with active disease. Ninety-one of the 117 patients, or 77.7 per cent, survived 1 year and this would indicate a good or excellent response to the treatment.

Osgood and Seaman[25] used total body spray irradiation or P^{32}. They gave maintenance treatment at regular intervals whether the patient had symptoms or not in an effort to maintain a near normal clincial status. Lawrence *et al.*[17] injected intravenously 1–2 mc P^{32} once or twice a week for 4 to 6 weeks, usually not repeated within 6 months. They also used general supportive care as well as local roentgen therapy to the lymph nodes and spleen when they were enlarged and did not respond to a safe dose of radiophosphorus as described by Reinhard *et al.*[28] The indications for treatment were an increase in leukocytosis, increasing anemia or increase in the size of the lymph nodes or the spleen. Maintenance or prophylactic doses were not used. Osgood and Seaman[25] and Lawrence *et al.*[17] expressed the survival time from the onset of symptoms. The 1 year and 5 year survival figures are quite high when compared to our series which shows survival time from the initial treatment.

Tivey[39] reviewed the reported survival figures for a large number of patients with chronic leukemia through 1951 and found that half of the patients in any series comparably treated may be expected to survive 2.65 years after development of symptoms and 1.6 years after commencement of therapy.

Scott,[33] who like Bethell[4] used both chemotherapy and roentgen therapy, usually in combination, reported survival figures similar to ours but his results were determined from the onset of the disease. His survival figures are lower than those of Osgood and Seaman[25] or Lawrence and his colleagues.[17]

TABLE III

COMPARATIVE LONG TERM SURVIVAL PERCENTAGES WITH DIFFERENT MODALITIES OF TREATMENT

	Total No. of Cases	Survival Percentages				Treatment
		Years				
		1	5	10	15	
1954, Lawrence[18]	129	96	54	15	3.5	P^{32} alone or with roentgen rays
1957, Scott[33]	118	79	19.5	3.5		Radiotherapy and/or chemotherapy
1958, Osgood, Seaman, and Koler[24]	102	92.3	44.1	9.8	0.9	Titrated total body roentgen therapy
1959, Reinhard, Neely, and Samples[29]	102	77	51	14		P^{32} predominantly
1961, Cook and Romano*	117	77.7	30.3	12	5	Regional roentgen therapy

* Percentage survival rate is determined from initial treatment; in other series from onset of symptoms.

TABLE IV

COMPARISON OF SURVIVAL TIMES FOR LIVING AND DECEASED PATIENTS

	Total No. of Cases	Mean Survival (mo.)	Median Survival (mo.)
Deceased	103	45.2	29.6
Alive	14	80.3	69.6

Reinhard *et al.*[29] reported on 102 patients with adequate follow-up data out of a total group of 302 seen with chronic lymphocytic leukemia. Only those cases were included which had at least 3.0 mc of radioactive phosphorus (P^{32}) and survived for 1 month after the first treatment. The average patient had received 11.6 mc. Fifty-five per cent also had some roentgen therapy but the predominant therapeutic agent was radiophosphorus. The date of onset of the disease was taken from the date the diagnosis was established by an abnormal blood finding and the survival times were computed from this date not from the date of the first treatment. A mean survival time (after the method of Tivey[39]) of 42.4 months for the nonsurvivors and 78.3 months for the survivors was noted. Therapy was given when the white blood cell count was over 50,000 or when it was betweeen 25,000 and 50,000 per cu. mm. and the patient had active symptoms and physical signs such as hepatosplenomegaly, hematologic findings of anemia, an abnormal platelet count, or an increase in the immature cells of the peripheral blood.

Table IV shows the mean survival and median survival in our living and dead patients. The mean survival was 80.3 months for the living patients and 45.2 months for the expired patients; the median survival was 69.6 months and 29.6 months, respectively, which compares very closely with the figures reported by Reinhard *et al.*[29] The patient living the longest following the first treatment in our series had been followed for 21 years and 8 months and expired at the age of 62 years.

The prolongation of the average duration of life obtained by treatment of chronic lymphocytic leukemia is rather insignificant, perhaps one-third to one-fourth longer than expected in the untreated cases. However, the symptomatic improvement is remarkable and it is believed that the efficiency of the patient is increased by 60 per cent throughout the major part of the duration of this disease. This conclusion was reached by Leucutia[19] after a review of the literature up to 1934. We have found no reason to change this opinion.

COMPARISON OF ROENTGEN THERAPY AND CHEMOTHERAPY

Chemotherapy has been used rather recently so that, of necessity, only short term results have, as yet, been reported in any significant number of cases. For this reason the criteria for the usefulness of these agents must be based primarily on symptomatic improvement, increase in efficiency and objective signs of improvement rather than on survival times.

To gain a basis for possible comparison with roentgen therapy, the cases in our series were also evaluated for short term results (Table v). The cases were divided into three groups. I. Those considered to have an excellent response were the patients who had relief of the symptoms of weakness or pressure effects, whose blood picture returned to near normal or whose tumefactions decreased markedly and those who were able to return to a relatively normal life including their regular work. II. A good response included the group in which some

TABLE V

RESPONSE TO TREATMENT AFTER FIRST THREE MONTHS AND CONTINUED RESPONSE AFTER ONE YEAR

	No. of Patients Available	Group		
		I (Excellent)	II (Good)	III (Poor)
3 months	117	99	12	6
1 year	91	86	3	2

Table VI

RESPONSE WITH CHLORAMBUCIL AS REPORTED

	Year	Cases	Group		
			I (Excellent)	II (Good)	III (Poor)
Ultmann, Hyman, and Gellhorn[40]	1956	18	3	7	8
Doan, Wiseman, and Bouroncle[10]	1958	18		12	6
Israels, Galton, Till and Wiltshaw[15]	1958	27	12	9	6
Rundles *et al.*[32]	1959	23	3	14	6
Miller, Diamond, and Craver[21]	1959	19	6	6	7
Bethell, Meyers, Bishop, and Spencer[5]	1959	47	Satisfactory 41		Unsatisfactory 6

evidence of improvement was manifested as above with a decrease in the activity of the disease and improvement in general well-being so that a 50 per cent or more return to normal activity was possible. III. The third group consisted of those patients who showed no response to treatment or a response of lesser degree than that in the first two groups of patients. There was either no appreciable increase in the patient's general well-being, or an actual loss.

Two sets of figures are presented: the first at the end of 3 months and the second at the end of 1 year. At the end of 3 months of treatment, 99 patients were thought to have had an excellent response, 12 a good response and only 6 a poor response. After therapy and careful supervision for 1 year, 86 maintained an excellent response, 3 a good response and 2 showed a poor response.

Table VI is compiled from several reports in the literature of the response obtained to chlorambucil (CB 1348). These patients were treated with daily doses of 0.1 to 0.2 mg./kg. body weight in courses ranging from 3 to 4 weeks to several months. Generally, the patients were re-evaluated after 3 to 4 weeks of treatment in order that the dosage might be reduced. Rundles *et al.*[32] suggested that the results not be evaluated until after at least 3 months of trial therapy. Israels *et al.*[15] stated that if the patients did not respond in 6 weeks, increasing the dosage would be of no value. In analyzing the results, the patients usually were placed in three categories, there being some minor differences as to the criteria of evaluation by the various authors. In the first category were those with a good to excellent response, in the second those with slight to good response and in the third those with a poor response. Bethell *et al.*[5] simply state that of 47 cases 41 had a satisfactory response and 6 had an unsatisfactory response. A total of the results listed in Table VI of those patients responding in one group and those not responding in another group shows that of 152 patients treated with chlorambucil, 113 had some favorable response to therapy and 39 had poor or no response. These figures may be compared with those in Table V for the patient response to radiation therapy at the end of 3 months: 111 showing some favorable response and 6 a poor or no response.

Chlorambucil was chosen as the radiomimetic agent most suitable for comparison because it is considered by the majority of authors[1,4,8,9,11,14,21,32,40] to be the best among the present chemical agents for the treatment of chronic lymphocytic leukemia. It is too early for any significant number of long term results to be recorded but remissions and improvement have been reported lasting from 2 weeks to $3\frac{1}{2}$ years.[15]

Nitrogen mustard and triethylene melamine (TEM) have been used,[4,8,9,31] but no large series of cases have been reported.

Rundles and Barton[31] treated 23 cases with TEM over an 18 month period and reported 12 cases as having an excellent response and 6 a good response. Diamond[9] believed that these agents were useful only for their immediate effect in selected cases and should be followed by radiation therapy. Bethell[4] stated that maintenance therapy with TEM was difficult to establish and should be used with caution because of its myelotoxic effect which may develop after the drug is discontinued. Myleran has been found to be beneficial primarily in chronic granulocytic leukemia.

The corticosteroids have been used largely as an adjunctive agent in the treatment of chronic lymphocytic leukemia. Shaw *et al.*[35] reported 24 cases in which prednisone was employed. Seventeen of these completed a 3 month course. There was symptomatic improvement in all cases, but 70 per cent had recurrence of activity before treatment was completed or within 4 weeks after its completion. Bethell,[4] Dameshek and Gunz,[8] Shaw *et al.*[35] and others have suggested that corticosteroids have a limited value in the treatment of terminal cases and in the treatment of symptomatic hemolytic anemia, thrombocytopenia, purpura and those patients who have the autoimmune type of leukemia with a positive Coomb's test.

DISCUSSION

Chronic lymphocytic leukemia is treated by some clinicians as soon as the diagnosis is made and by others only when the disease is progressing or because of symptoms. After treatment is instituted, it may be continued once response is obtained at a maintenance level, or stopped until further increase in activity is noted. Each of these latter methods have their advocates and, as yet, no substantial gain in patient benefit has been proven by either group.

There is general agreement that life is prolonged by the treatment but the chief beneficial effects are: (1) objective improvement consisting in improvement of the anemic state, arrest of the tendency to hemorrhage, slowing down of the predisposition to infections, reduction of fever, stoppage of weight loss and regression in the size of tumors causing pressure or obstructive effects; and (2) subjective improvement such as shrinkage of disfiguring tumors, an increased sense of well-being and diminishing of lassitude. These effects, *i.e.*, the lengthening of life and the provision of a more normal way of life, can be obtained by different types of treatment. The patients included in our series have been treated only when active disease was present and retreated when the activity resumed following varying periods of remission. Administration of small doses of external roentgen rays had been the primary method and in most the only method of treatment. The long term results are compared with the long term results obtained by others using radiation therapy either delivered by external or internal means. No appreciable difference is noted in survival rates when all factors of choice of patient, date of compiling survival statistics and method of determining survival are compared.

More recently several relatively new chemotherapeutic regimens have been established, the most generally used being chlorambucil. When attempting to compare the response obtained by this agent with that of radiation therapy in our series, no particular advantage can be seen in the use of chlorambucil. The value of HN_2 and TEM has been somewhat disappointing to ourselves and others[8,9,10,14,15,21] because of the toxic and undependable effects produced. Their use as well as the use of corticosteroids has generally been noted to be beneficial only in special situations in the cases of chronic lymphocytic leukemia. This may also be said of splenectomy.

Because of the variable nature of chronic lymphocytic leukemia, external regional irradiation has perhaps greater value in the treatment of this disease than in the treatment of chronic granulocytic leukemia. There is agreement[5,8,9,33] that locally administered radiation therapy is more useful

than chemotherapy in the treatment of bulky tumor masses and hypersplenism. It would seem that, although a few cases responded to chlorambucil and not to irradiation[10,15,21] and vice versa,[10,21] the choice of a mode of therapy for short term response would likely be between irradiation and administration of chlorambucil. This choice should be made on the basis of benefit to and convenience of the patient. Chlorambucil therapy gives a better regulated response and less chance of bone marrow depression than the other drugs.[8,10,14,15,21] It does have the disadvantage of slow action[1,9,21,30] and occasional drug sensitivity.[5] External irradiation of the tumefactions or the skin lesions produces rather rapid effect so that lymphocytic tumors have long been described as "melting away" under this form of treatment. In those patients where a good response is elicited and aided by the chronicity of the disease as illustrated in Table 1, very little treatment is needed. In all cases and with all methods, careful routine follow-up by clinical and laboratory means is necessary. It is too soon to judge the long term response or effect on survival time of the new radiomimetic agents.

SUMMARY AND CONCLUSIONS

1. One hundred and fifty cases of chronic lymphocytic leukemia seen at Harper Hospital from 1922 through 1960 have been analyzed. The average age of the males was 56 years and of the females 58.4 years, giving a general average age of 56.7 years.

2. The amount of roentgen radiation delivered and the various survival times have been studied, and it has been definitely shown that those patients who survive longest need less therapy and have a more chronic type of disease or a greater natural resistance to its effects.

3. The results of external regional roentgen therapy in 117 patients with active disease have been presented both as to long term survival time and as to response at the end of 3 and 12 month periods. These results have been compared with those of similar series treated with other modalities as reported in the literature.

4. The survival rate has been found to be similar whether radiation has been given to the whole body by external means or P^{32}, or whether regional external irradiation has been used.

5. Median survival times for living and deceased patients have also been presented. No increase in longevity has been found in patients having received maintenance therapy.

6. Finally, an attempt has been made to compare the short term patient response to radiation therapy with that to the chemotherapeutic agents, particularly chlorambucil; and again no advantage was noted over that obtained with radiation therapy. In the case of chemotherapy it will be necessary to judge the long term results at a later date.

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ROENTGEN TREATMENT OF CHRONIC LEUKEMIA*

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THE work here presented was originally planned with the late Dr. Merrill C. Sosman, Harvard Medical School Professor of Radiology at the Peter Bent Brigham Hospital. It deals with certain data concerning 107 patients with chronic leukemia treated at the hospital by roentgen radiation for the most part in cooperation with Dr. Sosman until his retirement in 1956.

An attempt has been made to include in this group only those patients with chronic leukemia, although it is a well recognized fact that it may be difficult to distinguish the chronic form from the acute, or subacute, in some instances. Sixty of the group were classified as granulocytic and 47 as lymphocytic leukemia cases.

During the earlier years, as was the prevailing custom, and occasionally later, treatment was directed either to the spleen, the chest, the long bones, or masses of lymph nodes. Following a remission, treatment was usually withheld until another relapse occurred and the general condition of the patient was poor. The rather large doses of roentgen rays required were frequently followed by anorexia, severe nausea and vomiting and general malaise. After recovery from these, there was a short period with some degree of well being, followed by the next relapse, requiring another round of treatment.

It was observed, however, that treatment over the long bones only was followed by a satisfactory response of the leukocytes, but with less of the toxic effects so frequently observed following treatment to the spleen or chest. In view of these facts it was decided that the method of treatment would be modified in two major respects, in the belief that some of the unpleasant effects of therapy might be avoided, thus allowing the patient to live more normally and comfortably and possibly to have a longer life span.

METHOD AND MATERIAL

The first modification was to apply treatment in small dosage over the entire trunk from the mid-thighs upward at 1 meter distance alternating front and back, the so-called teleroentgen therapy. The second modification was to start treatments when the leukocyte levels tended to rise above 40,000 cells per cubic millimeter, rather than to wait for a more severe relapse, thus maintaining a rather uniformly near normal leukocyte level. This we decided to refer to as the spray technique, as opposed to the local application previously employed. Doses of from 15 to 50 or 60 r were given, depending upon the patient's condition and the effect anticipated. The method used was discussed in a paper published in 1940.[4]

The spray technique was introduced in the early part of 1934 and with few exceptions has been employed as the principal method of treatment since that time. Local treatment to masses of lymph nodes, or to the spleen, was given when it was indicated. In order to compare the relative effects of the spray and local techniques, the patients treated by each method are considered separately according to the predominating technique used. Thirty-nine patients with granulocytic and 32 with lymphocytic leukemia were treated by the spray technique; 21 with granulocytic and 15 with lymphocytic leukemia received only local treatment. A few of each group also received some form of chemical therapy at sometime during their illness.

The patients with granulocytic leukemia were divided equally in respect to sex; in the lymphocytic group there were 27 male and 20 female patients. The age at onset,

* Read before the Tenth Congress of Nobel Prize Winners on July 5, 1960 at Lindau im Bodensee, Bavaria, Germany.

Table I

AGE DISTRIBUTION OF 107 PATIENTS WITH CHRONIC LEUKEMIA

Age at Onset* (decade)	Lymphocytic Group No. of Patients	Granulocytic Group No. of Patients
20–29		3
30–39	2	17
40–49	4	14
50–59	21	14
60–69	16	6
70–79	3	4
80–89	1	2
	47	60
Age Extremes (years): Low	36	23
High	82	85

* First definite signs or symptoms of leukemia.

the first definite signs or symptoms recognized as manifestations of the disease, differed somewhat in the two groups. The onset occurred before the fifth decade in more than half of the granulocytic group, but in only 6 of the lymphocytic group. The onset occurred in the eighth decade in 1 patient of the lymphocytic group, as compared to 2 in the granulocytic (Table 1).

RESULTS AND MANAGEMENT

The number and percentage of three, four, five and seven year survivors in both the lymphocytic and granulocytic group according to the treatment method are given in Table II and Figure 1. The percentage of patients surviving three years is approximately the same whether treated by spray or local techniques in both varieties of leukemia. Twenty-five or 78 per cent of the 32 lymphocytic leukemia patients treated by the spray method and 12 or 80 per cent of the 15 treated locally survived three years. Of the 39 granulocytic leukemia patients treated by spray, 23 or 59 per cent and of the 21 treated locally 13 or 62 per cent survived three years. Thereafter, in those with lymphocytic leukemia there is considerable difference between the survival time of those treated by the two techniques. At four years survival, the comparable figures to those recorded above are 22 or 69 per cent by the spray technique, 9 or 60 per cent by local treatment; at five years 19 or 59 per cent by the spray technique, 4 or 27 per cent by local treatment; and at seven years 15 or 47 per cent by the spray technique, 3 or 20 per cent by local treatment. Of those with granulocytic leukemia 14 or 36 per cent treated by the spray technique and 3 or 14 per cent treated locally survived four years. At five and seven years there was no difference in the percentage of survivals. Table III shows that the average survival in the lymphocytic group treated by the spray method was 6.6 years, by local treatment 4.6 years. In the granulocytic group, the figures are respectively 3.1 and 2.8 years. Fractions of years

Table II

NUMBER AND PERCENTAGE OF PATIENTS SURVIVING THREE, FOUR, FIVE AND SEVEN YEARS

Years of Survial	Lymphocytic Group (47 patients)				Granulocytic Group (60 patients)			
	Spray Treatment		Local Treatment		Spray Treatment		Local Treatment	
	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent
0	32	100	15	100	39	100	21	100
3	25	78	12	80	23	59	13	62
4	22	69	9	60	14	36	3	14
5	19	59	4	27	4	10	2	10
7	15	47	3	20	2	5	1	5

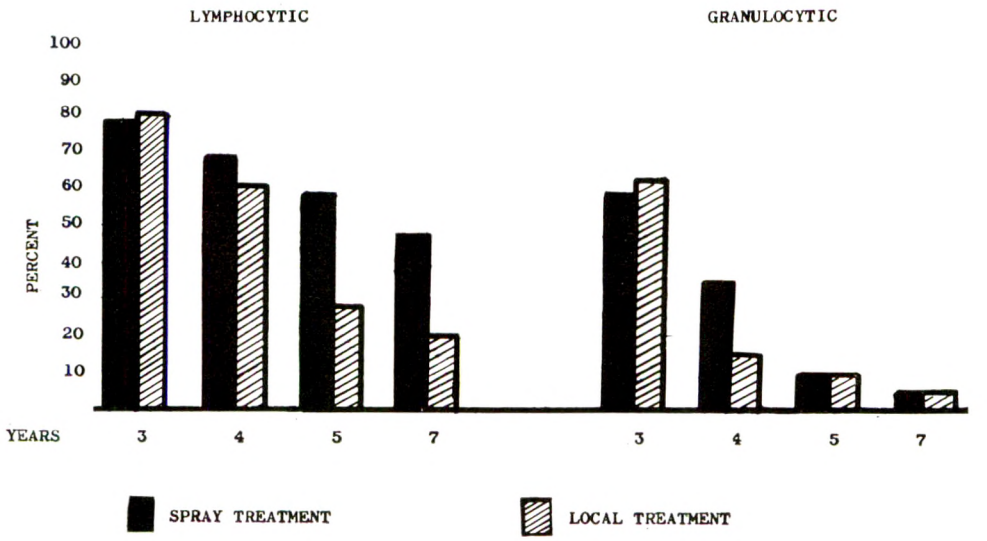


FIG. 1. Percentage of patients surviving three, four, five and seven years.

have been avoided in recording survival time by using the nearest year, that is above or below six months as observed.

TABLE III

SURVIVAL TIME FROM ONSET*

Years of Survival	Lymphocytic Group		Granulocytic Group	
	Spray Treatment	Local Treatment	Spray Treatment	Local Treatment
	No. of Patients	No. of Patients	No. of Patients	No. of Patients
1	1	2	6	3
2	6	1	10	5
3	3	3	9	10
4	3	5	10	1
5	3	1	2	
6	1†			1
7	5			1
8	1			
9	1		2	
10	3	2		
11	1†	1		
12	1			
16	1			
17	1			
26	1			
Average	6.6	4.6	3.1	2.8 years

* First definite signs or symptoms of leukemia.
† Still living.
This table shows the survival time from onset and the type of treatment for each of the 107 patients reported in this study.

Moffitt and Lawrence[3] have recorded from their own experience and from the literature 31 instances of survival from onset of symptoms of more than five years. The longest survival, 25 years, was reported by McGavran.[2] It is of interest to note that in our series, all with lymphocytic leukemia, 5 survived ten years, 2 eleven years and 1 each twelve, sixteen, seventeen and twenty-six years. Two with granulocytic leukemia survived nine years (Table III).

The figures indicating survival time shown in Tables II and III compare favorably with those recorded in previously reported series. They also suggest some advantage in duration of survival time for those treated by the spray method as opposed to local technique, although this advantage is not striking. There has been, however, a great difference between the effects of the two techniques in respect to the condition of the patients during their illness. Those treated with large dosage locally over the chest or spleen, and at the time of severe relapse, have, as previously noted, experienced periods of rather disturbing malaise, anorexia, nausea and vomiting after treatment, with only brief periods of well being between treatments, whereas those treated with the small dosage by the spray technique have suffered

few ill effects as the result of treatment and have, in general, lived normal lives, carrying on their usual occupations throughout their period of illness. The mild anorexia or nausea which occasionally followed this treatment was usually controlled or avoided by intramuscular injections of 50 to 100 mg. of pyridoxine hydrochloride. Those who had experienced anorexia or nausea were treated in this manner an hour or two before roentgen therapy with excellent effect.

It may be profitable to record briefly the regimen recommended for the management of treatment in the patient after the diagnosis has been established. This will, of course, vary, depending on many circumstances. If the leukocyte level is high the patient, with all pertinent data regarding history and blood picture, is referred to the radiologist for treatment. The spray treatment may be applied daily or on alternate days and must be controlled by leukocyte counts before each exposure. Pyridoxine should be injected before each treatment if indicated. Treatment is continued in small dosage until the leukocyte level has dropped to 30,000, or perhaps lower depending upon the rate of drop. As one may expect the count to continue to drop for several days after treatment is stopped, it is desirable to check the count in about a week as a guide to subsequent courses of treatment. The patient should be seen and the count checked thereafter every four to six weeks. When there is again a tendency for the leukocytes to increase, one or more treatments may be sufficient to return the count toward normal. In this way an attempt is made to maintain fairly uniform and near normal leukocyte levels. This method of treatment, always carried out in consultation between physician and radiologist, is used for control of the leukocytes though massive enlargement of lymph nodes may require local therapy for their control. Rarely will it be necessary to treat locally for enlargement of the spleen, provided the spray treatment is carried out regularly, for this will tend to control its size.

If the leukocyte level is not high when the diagnosis is made, treatment should be delayed until the level rises sufficiently to indicate the need for control. For example one of our patients with lymphocytic leukemia was followed for five years before treatment was started. He survived seven years after starting treatment, a total of twelve years, and died after a myocardial infarction at a time when the leukemia was well controlled. If lymph node enlargement is the presenting problem, local application rather than spray treatment will be indicated. This situation is illustrated by another patient with lymphocytic leukemia. His complaint was of deafness which his aurist thought might be caused by pressure from enlarged lymph nodes in the cervical region. The leukocyte count was only slightly increased. Local therapy reduced the lymph node mass and cured his deafness. Subsequently, spray treatment became necessary and he remained in excellent health for two years. He would undoubtedly have had a long survival, even though he was seventy-two years of age, had circumstances been more favorable. Death followed a severe hemorrhage from the gastrointestinal tract which occurred during a severe storm in the middle of winter at his farm in Canada which was twenty miles from the nearest medical assistance. The history indicated that the hemorrhage was from a duodenal ulcer and not related to the leukemic condition.

The results of treatment in the granulocytic group have not been as satisfactory, in general, as in the lymphocytic group, and yet the majority of patients have been remarkably well and able to carry on their usual activities throughout most of their illness. An example of a well controlled patient with granulocytic leukemia is that of a forty-seven year old model maker in a brass foundry whose leukocyte levels were maintained between 5,000 and 40,000 for three and a half years during which time he continued at work and in excellent health. A few days before death he complained of severe pain in his head and abdomen, the

TABLE IV
CAUSE OF DEATH

	Lymphocytic Group		Granulocytic Group		Total
	Spray Treatment	Local Treatment	Spray Treatment	Local Treatment	
Pneumonia	7	1	4	0	12
Cerebrovascular	0	2	5	3	10
Multiple Infarcts	1	0	8	1	10
Myocardial Failure	4	1	1	1	7
Myocardial Infarct	3	0	0	1	4
Hemorrhage	3	0	3	2	8
Sepsis	2	1	1	2	6
Tuberculosis	1	2	1	1	5
Malignant Disease	0	1	1	0	2
Renal Failure	0	0	1	0	1
Result of Treatment	2	1	1	1	5
Leukemia	7	6	13	9	35
	30	15	39	21	105*

* Two of the 107 patients in this study are living.

urine contained an excessive amount of sugar, he became comatose and died a few days later after being hospitalized for the first time. Postmortem examination showed a cerebral thrombosis as the cause of death.

Unfortunately, a few of our patients were not available for, or did not, for one reason or another, follow up treatment in the prescribed manner so that the best possible results were not obtained. This undoubtedly shortened the survival span in some instances and thus influenced the average.

The causes of death, as observed in this series, are interesting, particularly as they indicate that more than half of the patients died from diseases not directly related to leukemia. Two patients with lymphocytic leukemia are living and in excellent condition six and eleven years respectively after onset.

Of the 105 patients who have died, the cause of death in 69 has been established as other than leukemia. Postmortem examination confirmed the cause of death in 35 of this group. Perhaps those who died of pneumonia or hemorrhage, for example, should be included with those who died from a disease directly related to leukemia (Table IV). The cause of death for 35 patients is recorded as due to leukemia. Those with severe hemolytic anemia, localized infection, progression of the leukemia due to refusal of therapy, and a few in whom no other cause could be determined are included in this group.

Pneumonia was considered to be the cause of death in 12 patients, the most frequent single cause. However, 21 patients died of cardiovascular disease and, if one considers all of the cardiovascular group together, this is by far the greatest number. It is also of interest to note that of the 10 patients who died from multiple infarcts, which included splenic infarction, 9 were in the granulocytic group. Five deaths are recorded as due to unfavorable effects of treatment. One died of post-transfusion shock after receiving incompatible blood in another hospital. The other 4 patients died of complications directly resulting from chemotherapy. Death followed the use of TEM, nitrogen mustard, aminopterin and urethane in one patient each. The patient treated with urethane also received ACTH intravenously. Four other patients died after severe bone marrow depression following chemotherapy, but the causes of death are otherwise recorded in Table IV—

2 under pneumonia, 1 cerebral vascular accident and 1 myocardial infarction. Again 4 different chemicals were responsible—nitrogen mustard, TEM, mercaptopurine with cortisone and myleran each in one patient. The chemotherapy was not carried out by the authors.

A solution of potassium arsenite (Fowler's solution) was used in a number of instances, particularly during the earlier years, but was discontinued because of its unpleasant side effects. One patient with granulocytic leukemia had received Fowler's solution for two years when first seen by us. At no time during this period of treatment had he been free from severe anorexia, malaise and nausea so that he had lost forty pounds of weight and refused to continue treatment. After he was started on spray radiation therapy, he had no further difficulty and regained the forty pounds within a few weeks. He lived comfortably for two more years.

The published results of chemotherapy have not been sufficiently impressive to induce us to abandon spray roentgen therapy in its favor. Because we have had little personal experience with the use of chemicals, other than Fowler's solution, it is not our intention to attempt to evaluate the comparative effects of roentgen versus chemotherapy. A brief record of the experiences of some of our patients who received chemotherapy, elsewhere than under our direction at some time during their illness, may be of interest and instructive. Twelve patients, in addition to the 8 mentioned above, have received one or more chemicals for varying periods of time. Urethane was discontinued after short periods of trial in 6 patients because of severe anorexia with nausea and vomiting. It was tolerated, but had little clinical effect in 1 patient. TEM was discontinued in 1 patient because of anorexia and nausea, and in another after twice causing severe leukopenia. This patient died of pulmonary tuberculosis shortly after the last trial. Aminopterin was used once but stopped because of unfavorable effects. Cortisone was given to 4 patients, 2 of whom also received antibiotics. Two of these died of miliary tuberculosis, one after a year of use, the other after a few weeks of use together with an antibiotic. One died of septicemia while taking cortisone and an antibiotic; the fourth of a cerebral vascular accident three weeks after starting cortisone.

These unfavorable experiences with chemotherapy are not sufficient to condemn this method, particularly in view of the fact that it has been employed in a few instances in which the disease may have been in a terminal stage regardless of the therapy used. However, in comparison with the absence of toxic effects following the application of roentgen rays in small dosage by the spray technique and because of the lack of evidence of superiority of chemotherapy over that of spray irradiation in reports thus far available, one may question the advisability of further experiment with the chemicals presently in use. The corticosteroids may be of value in some instances in conjunction with roentgen therapy, particularly for control of hemolytic anemia. The patient receiving a corticosteroid should also receive an antibiotic and be watched closely for the presence of an infection because of the low resistance to infections so commonly present in leukemia patients.

Lawrence[1] has reported favorable results with the use of P^{32} and Osgood *et al.*[5] have compared the effects of P^{32} with those of spray therapy, showing no definite advantage of one over the other. Where spray therapy is available, it would seem to be the treatment of choice for the patient with chronic leukemia.

CONCLUSION

Research during the past forty years has not produced a strikingly important development for the treatment of chronic leukemia. Perhaps the most significant development has been the introduction of the spray method of roentgen irradiation as used in this series of patients, which has tended to minimize some of the unpleasant

side effects of therapy, and so allowed the patients to live more comfortably and normally throughout their illness. There may also have been added a few years to the life span and even more may be possible now that infections may be controlled with the use of the sulfonamides and antibiotics. The majority of the patients in this series was treated before these were generally available.

Anemia has been a frequent and important complication as might be expected. Transfusions have been given when indicated. Not only have they increased the life span, but have added much to the comfort and well being of the patient. Both iron and injections of either liver extract or vitamin B_{12} have been used in some patients for the control of anemia with seemingly beneficial effect, although improvement of the blood levels was frequently observed following irradiation alone.

Experimental work in the future, in order to be successful in the management of leukemia, whether acute or chronic, must be directed toward finding a means of encouraging normal production or maturation of leukocytes rather than their destruction, or toward prevention of the disease by recognition of those factors which may initiate the abnormal growth of cells so that these may be avoided.

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THE RADIOTHERAPEUTIC MANAGEMENT OF THE LYMPHOMATOUS DISEASES*

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THE radiotherapeutic management of the squamous cell carcinomas and the radiosensitive adenocarcinomas has reached a moderate degree of standardization throughout the world. This standardization is based on clinical factors defined in the terms of: the primary lesion, the patterns of spread to regional lymph nodes, data on cancerocidal dose levels, and, finally, the anticipated results of treatment. Success is measured in terms of "cure rates," and is predicated on the eradication of the local lesions and the regional lymph node metastases, prior to the development of distant metastases.

By contrast, because of the lack of systematic patterns of spread and clinical behavior, widely divergent views are held on the management of the lymphomatous diseases. In any series of patients with lymphomatous diseases, a fair percentage presents with generalized disease. Although apparently localized or semilocalized initially, in the majority of the cases the disease eventually becomes generalized. In the acute and semiacute forms of the disease, this generalization is sufficiently rapid and erratic to suggest the presence of a tumor-inducing factor throughout the entire lymphatic system. In some more chronic forms of the disease, it would appear, at least in the early stages, that the process of spread may be by the regional lymphatic channels; however, even in the chronic cases, the appearance of new areas of involvement may be haphazard.

In the squamous cell carcinomas and the radiosensitive adenocarcinomas, the incidence of metastases is unquestionably reduced by control of the primary lesion. In contradistinction, conclusive proof is lacking that control of the local areas of involvement lengthens the periods of remission in the lymphomatous diseases.

There are two schools of thought on the radiotherapeutic management of the lymphomatous diseases. One approach, based on the opinion that the lymphomatous diseases are multicentric in origin, is to administer radiation sufficient only to effect a temporary remission of the local tumor, repeating the therapy when necessary. The other approach calls for irradiation, delivered to entire anatomic regions, sufficient enough to prevent regrowth at local sites. A logical extension of this concept of treatment is to irradiate the surrounding regions prophylactically, in the hope that prophylactic treatment will contribute to longer periods of remission.

It is the purpose of this paper to review the radiation management of the lymphomatous diseases in this institution with emphasis on: (1) the geometric techniques and tumor dose levels, by stages and by anatomic regions; (2) the local results of treatment in terms of tumor doses by stages and by anatomic regions; (3) the advantage of supervoltage therapy in the management of disease in certain anatomic regions; (4) the relationship of histologic type of disease to the management of that disease by irradiation; (5) the hypothesis that vigorous treatment to the local areas of involvement lengthens the intervals of remission; and (6) the hypothesis that pro-

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phylactic treatment to adjacent regions may also contribute to longer periods of remission.

MATERIAL

The charts of 278 patients with lymphomatous diseases, admitted from April, 1947 through July, 1959, have been analyzed to determine the physical status of each patient as of July, 1960. All patients were treated by radiation therapy, or by a combination of radiation therapy and chemotherapy. Excluded from study were 44 cases which were treated exclusively by chemotherapy. Also excluded from this series were patients with multiple skin, subcutaneous, or bone lesions, bone marrow involvement, cases of uncertain pathology, and those who later developed leukemia. None of these cases was considered suitable for analysis from the standpoint of results of treatment by radiation therapy.

Of the 278 patients, 239 were white, the remainder were Latin American or Negro. In all 3 races, the usual male sex incidence predominated. There were 161 males and 117 females. Although the lymphomatous diseases are generally considered to be diseases which afflict young people, in this series the incidence was greatest in the 50 to 70 year bracket (Table I).

HISTOLOGY

There were 106 cases of lymphosarcoma and 94 cases of Hodgkin's disease; the remaining 78 cases were fairly evenly distributed between the giant follicular lymphomas, the reticulum cell sarcomas, and the unspecified lymphomas. A comparative study of the lymphomatous diseases would suggest that Hodgkin's disease has a considerable tendency to evolve from a localized or a semilocalized state to a generalized process (Table II). By contrast, the other lymphomatous diseases tend to by-pass the intermediary semilocalized state when progressing from a localized to a generalized form.

TABLE I

AGE DISTRIBUTION IN RELATION TO STAGE OF DISEASE

Age	Stage I	Stage II	Stage III	All Stages
00–09	1	1	2	4
10–19	7	6	5	18
20–29	20	11	6	37
30–39	15	11	8	34
40–49	17	8	12	37
50–59	34	7	24	65
60–69	22	5	27	54
70–79	13	4	8	25
80–89	2	—	2	4

STAGE

The method of staging, devised by Peters and Middlemiss,[5] was used in classifying our material. Data on specific organ involvement were recorded under appropriate stage and region. Stage I refers to disease localized to one region; Stage II, to disease localized to two or more contiguous regions, in either the upper or lower torso; and Stage III, to generalized disease. Of the 278 cases reviewed, the disease was apparently localized in 131, semilocalized in 53, and generalized in the remaining 94 cases (Table III). However, it appears from follow-up examination, that more patients had generalized involvement when first seen than originally recognized. By comparing cases of earlier years with those of more current years, it can be demonstrated that abdominal involvement is now being discovered more frequently at the time of the initial investigation. This can be explained by the more prevalent use of intravenous and retrograde pyelographic examinations, gastrointestinal series, lymphangiography, liver function tests, and hematologic studies.

POLICY OF MANAGEMENT

The volume of tissue to be irradiated in relation to the tumor dose is a critical factor in the management of the lymphomatous diseases. Although lymphomatous masses will frequently disappear following a tumor dose in the order of 1,000 rads, this dose will seldom produce permanent control of the local lesion. Tumor doses in the

TABLE II

HISTOLOGIC DISTRIBUTION BY STAGE

	Stage I								Stage II				Stage III	
	Total	Head and Neck	Head and Neck (Per Cent)	Axilla	Abdomen	Inguinal Region	Miscellaneous	Stage I (Per Cent)	Upper Torso	Lower Torso	Stage II (Per Cent)	Stage I and II (Per Cent)	Generalized	Stage III (Per Cent)
Hodgkin's Disease	94	22	25	8	1	4	—	36	37	—	39	75	22	25
Lymphosarcoma	106	22	20	4	11	7	8	50	9	2	10	60	43	40
Reticulum Cell Sarcoma	33	9	27	2	6	1	2	60	—	—	—	—	13	40
Giant Follicular Lymphoma	22	5	22	2	1	3	—	50	2	—	10	60	9	40
Lymphoma Not Specifiable	23	9	40	—	3	1	—	57	3	—	13	70	7	30

order of 3,000 to 5,000 rads are required for permanent control.[1,3,4,5] However, because of the limitation of the systemic tolerance, it is not always possible to achieve these dosage levels. The doses used in this institution for the three stages of disease are a result of a gradual evolution to our present concept of acceptable dosage levels. For Stage I disease, it is usually possible to administer doses in the order of 3,000 to 4,500 rads with orthovoltage equipment. However, treatment to the three major areas, *i.e.*, the head and neck, the mediastinum, and especially the abdomen, is much better tolerated if treatment can be given with supervoltage equipment. In some regions somewhat higher dosage levels can be given with a supervoltage unit.

For Stage II disease, our policy has been to use the same radical approach as in Stage I disease. To avoid exceeding the tolerance of the daily integral dose, treatment is frequently given to the major areas in series rather than concurrently. Critical areas are treated first.

Prophylactic treatment is used in some

TABLE III

INCIDENCE OF INVOLVEMENT BY REGION FOR STAGES I, II, AND III

Stage I		Stage II		Stage III	
Head and Neck	67	Upper Torso (excluding lung involvement)	45	Abdomen, Mediastinum and Peripheral Areas	36
Mediastinum	1	Upper Torso (with lung involvement)	6	Abdomen and Peripheral Areas	32
Axilla	16	Lower Torso	2	Mediastinum and Peripheral Areas	8
Abdomen	22			Peripheral Areas Only	18
Iliac and Inguinal Region	16				
Miscellaneous	9				
Total	131	Total	53	Total	94
Constitutional Symptom	4	Constitutional Symptom	6	Constitutional Symptom	19

TABLE IV

STAGE I—HEAD AND NECK

	Disease Restricted to Lymph Node Involvement	Involvement of Waldeyer's Ring or Paranasal Sinuses
Hodgkin's Disease	20	2
Lymphosarcoma	10	12
Reticulum Cell Sarcoma	3	6
Giant Follicular Lymphoma	5	—
Lymphoma Not Specifiable	4	5
Total	42	25

instances in Stage I and Stage II disease. Prophylactic treatment to the supraclavicular fossa is given for disease originating in the mediastinum or the axilla. Similarly, prophylactic treatment is given to the mediastinum for disease originating in the supraclavicular fossa.

For Stage III disease, the degree of radical therapy depends on the total volume of tissue involved and the general condition of the patient. Because of the complexities associated with generalized disease, further discussion of our treatment policy is deferred to the section on Stage III disease.

STAGE I

HEAD AND NECK

Sixty-seven cases of Stage I disease originated in the head and neck region. The development of treatment techniques for this site was influenced by histology and by anatomic extensions of the disease. Involvement of Waldeyer's ring is almost negligible in Hodgkin's disease, but is appreciable in the other lymphomatous diseases (Table IV). For all lymphomatous diseases, other than Hodgkin's disease, Waldeyer's ring is included, even when not clinically involved, in the treatment fields covering the neck and supraclavicular fossae. In irradiating the head and neck area, it is frequently necessary to modify the techniques somewhat to suit the individual patient.

Prophylactic treatment to the mediastinum is recommended in all instances with involvement of the lower neck or the supraclavicular fossae. Prophylactic treatment to the mediastinum is given either concurrently or later, depending on the total tissue volume under treatment, *i.e.*, on whether Waldeyer's ring is included in the treatment fields.

Treatment for Hodgkin's disease in the neck, if administered with orthovoltage equipment, is delivered with the head angled approximately 45° from the supine position (Fig. 1 *A*). For disease limited to one side of the neck, a dose of 3,000 to 4,000 rads, given at a rate of 1,000 rads per week, is generally well tolerated. When treatment is required for both sides of the neck, either concurrently or serially, the daily dose should be reduced to 150 rads to avoid exceeding the local tolerance of the midline structures. Bilateral involvement of the neck is better managed with supervoltage, using an anterior "split field" approach (Fig. 1 *B*). This technique will permit a given dose of 1,000 to 1,250 rads per week, up to a total dose of 3,000 to 4,500 rads, at a rate of 1,000 to 1,250 rads per week. A booster dose for residual disease persisting after a dose of 3,000 to 4,500 rads is added through reduced fields. With orthovoltage equipment, this additional treatment is given at a rate of not more than 250 rads per day for a total given dose of 500 to 1,000 rads. With supervoltage equipment a daily dose of 500 rads can be tolerated up to a total dose of 1,000 to 2,000 rads.

The irradiation techniques for the lymphomatous diseases, other than Hodgkin's disease, are designed to cover the nasopharynx in addition to both sides of the neck and the supraclavicular fossae (Fig. 2, *A* and *B*). Although therapy can be administered with a 250 kv. unit, supervoltage therapy is much better tolerated from the standpoint of both the local reaction of the tissues and the systemic tolerance. The maximum tumor dose per week for the average case will be 750 rads by orthovoltage or 1,000 rads by supervoltage therapy. The final tumor dose depends upon the

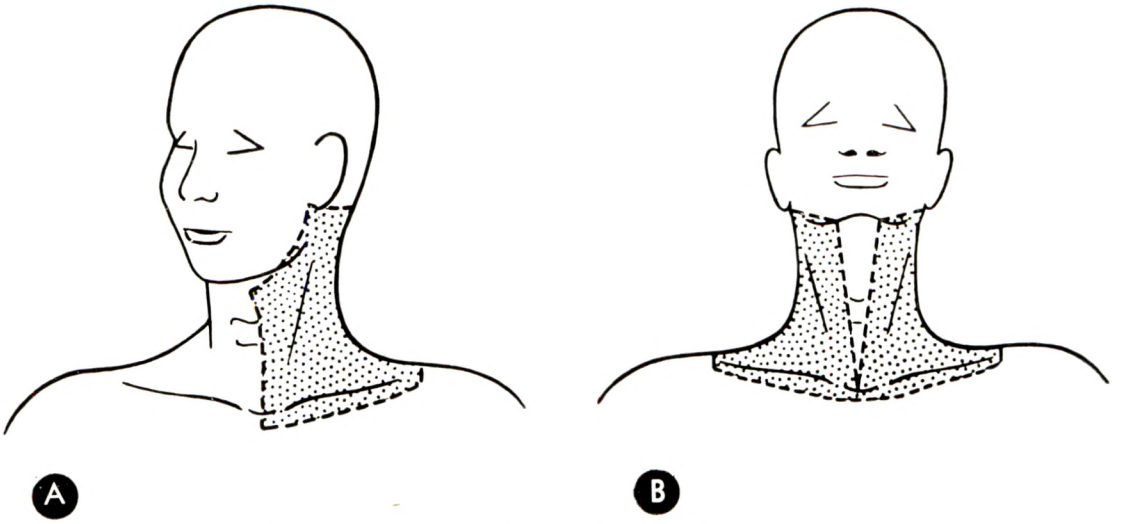


Fig. 1. (*A* and *B*) Therapy Fields for Hodgkin's Disease of the Neck.

Technique for 250 kv. Unit. The patient is placed in the supine position with the head rotated to 45° or more. Boundaries include the anterior and posterior cervical chains, the lower pole of the parotid gland, the tip of the mastoid process, and the lower border of the clavicle. The beam is allowed to "fall off" posteriorly.

Dose: 200 rads given dose per day to one side of the neck, *i.e.*, 1,000 rads per week; 150 rads given dose per day to both sides of neck, *i.e.*, 750 rads per week.

Total Dose: 3,000 to 4,000 rads, with a booster dose for residual disease.

Technique for Co^{60} Unit. The patient is placed in the supine position, with the head extended so that the superior border of the beam follows a line drawn from the chin through the angles of the mandible and the mastoid processes. The midline structures are shielded. Depending on the extent of the upper neck involvement, this shielding may be open or closed above the thyroid cartilage. The beam should "fall off" laterally.

Dose: 200 to 250 rads per day, *i.e.*, 1,000 to 1,250 rads given dose per week.

Total Dose: 3,000 to 4,500 rads, with a booster dose for residual disease.

histology, the fractionation of the dose, the rate of resolution of the tumor, and the specific location of the tumefaction.

Except for reticulum cell sarcomas and perhaps lymphocytic lymphosarcomas, there is no detectable difference in the dose required for permanent eradication of the disease. The reticulum cell sarcomas generally require higher doses than the other lymphomas; therefore, to achieve a tumor dose in the order of 5,000 rads, supervoltage therapy should be used. Frequently, a booster dose will be required for residual disease, particularly if it involves the base of the tongue. In contrast to the reticulum cell sarcomas, the lymphocytic lymphosarcomas are apt to be relatively sensitive. Frequently, a tumor dose in the order of 3,000 rads is sufficient for local control. But when fractionation of the tumor dose is less than 1,000 rads per week, or when the original tumefaction is massive, a dose of at least 4,000 rads should be administered regardless of the rate of regression.

For prophylaxis, the dose to the nasopharynx or the supraclavicular fossae need not be more than 3,000 rads given in approximately 3 weeks. A prophylactic tumor dose of 2,500 rads is usually given to the mediastinum if the lymphomatous process involves the middle or lower areas of the neck, or the supraclavicular fossae. When concurrent supervoltage treatment is delivered to the mediastinum, a tumor dose of 1,000 rads per week can usually be sustained. When orthovoltage is employed, tumor doses of no more than 750 rads per week should be attempted.

Results of Treatment to the Head and Neck. Of the group of 25 patients with malignant

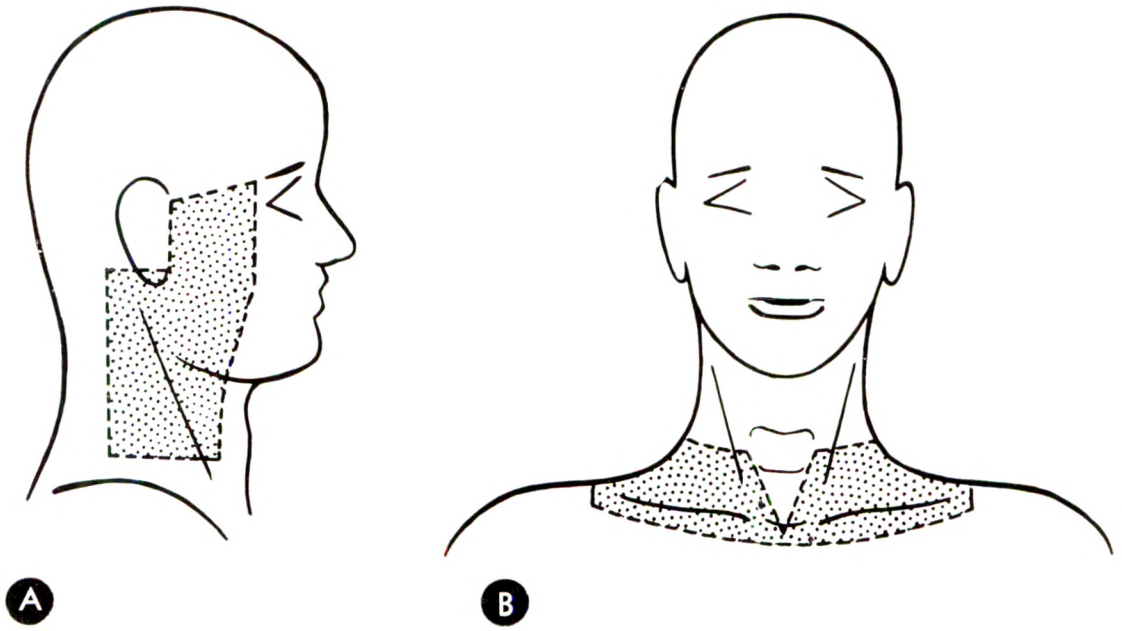


FIG. 2. (*A* and *B*) Therapy Fields for Lymphomatous Diseases Other Than Hodgkin's Disease of the Head and Neck Using a 250 kv. Unit or Co^{60} Unit.

(*A*) *Lateral Fields.* The patient is placed in the lateral position with the sagittal plane of the head in a straight line with that of the body. The borders of the fields are drawn to include the base of the skull, the posterior choanae, the posterior pharyngeal wall, and the anterior and posterior cervical chains. To ensure adequate coverage of the posterior pharyngeal wall (while avoiding treatment to the external auditory canal), the lateral field is tilted 5° posteriorly.

Tumor Dose: 250 kv. unit—150 rads per day, *i.e.*, 750 rads per week. Co^{60} unit—200 rads per day, *i.e.*, 1,000 rads per week.

Total Tumor Dose: 250 kv. unit—3,000 to 4,500 rads. Co^{60}—3,000 to 5,000 rads. A booster dose is added for residual disease for either unit.

(*B*) *Anterior Fields.* The patient is placed in a supine position. The borders of the field are drawn to cover the root of the neck and the supraclavicular fossae. An anterior "split" is used to protect the midline structures. The beam is allowed to "fall off" laterally and along the superior margin of the supraclavicular fossae.

Given Dose: 250 kv. unit—150 rads per day, *i.e.*, 750 rads per week. Co^{60} unit—200 rads per day, *i.e.*, 1,000 rads per week.

Total Dose: 250 kv. unit—3,000 to 4,500 rads. Co^{60} unit—3,000 to 5,000 rads. A booster dose is added for residual disease for either unit.

involvement of Waldeyer's ring, the disease was controlled in the ring in 23. In 18 patients, the lymph nodes of the neck, in addition to Waldeyer's ring, were also involved. The disease was controlled in the neck in 14 (Table v). An analysis of the cases in which the lymphomatous disease was confined to the neck revealed that local control was obtained in 70 per cent (Table vi). Of the 12 patients with local recurrence, 11 were deceased within one year. The 5 year survival rate for the entire Stage 1 group with involvement of the head and neck is 44.8 per cent, with a standard error of 6.8 (Table xii).

Results of Prophylactic Treatment to the Mediastinum. Of the group of 25 patients with involvement of Waldeyer's ring, very few received prophylactic treatment to the mediastinum. Because the majority were treated by the 250 kv. unit, the treatment was sufficiently taxing to preclude prophylactic irradiation.

A group of 42 patients with disease confined to the neck was analyzed according to whether the disease involved the upper or

TABLE V

STAGE I—HEAD AND NECK—WALDEYER'S RING, ETC.

Total No. 25 Waldeyer's ring or paranasal sinuses only—7 Waldeyer's ring, etc. and neck lymph nodes—18		Clinical Evolution		Duration (yr.) 1	2–4	5	6–9	10
Treatment:								
250 kv.	16							
Co^{60}	9							
Local Control	20	Alive—no distant exacerbations	10	2	3	4	1	
		Deceased—other causes	2	1	1			
		Deceased—distant exacerbations	8	6	2			
Local Failure	5	Alive—no distant exacerbations	1		1			
		Alive—distant exacerbations	1		1			
		Deceased—distant exacerbations	3	3				

Local control in Waldeyer's ring was obtained in 23 of 25 cases.
Local control in the neck was obtained in 14 of 18 cases.

lower neck. One of 10 patients with disease confined to the upper neck received prophylactic treatment to the mediastinum. Seven of the 10 are alive and well, 3 for approximately 2 years, 3 for a period of 2 to 5 years, and 1 for 9 years.

Of 32 patients with involvement of the lower neck, 17 received prophylactic treatment to the mediastinum. Of these, 11 have remained completely free of disease; 3 additional patients have remained free of disease in the local area and in the mediastinum, but have developed other manifestations of disease. Another 3 patients developed recurrence in the local site together with the appearance of involvement of the prophylactically treated mediastinum. Of 15 patients who did not receive prophylactic treatment to the mediastinum, all developed distant manifestations of disease. The majority of these patients are deceased. It would appear that prophylactic therapy of the mediastinum is of definite value in Stage I disease if the lymphomatous disease involves the lower neck or the supraclavicular fossa.

AXILLA

There were 16 cases with axillary involvement in the Stage I group. The majority of these cases were treated with the

TABLE VI

STAGE I—NECK LYMPH NODES ONLY

Total No. 42		Clinical Evolution		Duration (yr.) 1	2–4	5	6–9	10
Treatment:								
250 kv.	31							
Co^{60}	11							
Local Control	30	Alive—no distant exacerbations	19	6	10	2	1	
		Alive—distant exacerbations	3	1	1		1	
		Deceased—distant exacerbations	8	7	1			
Local Failure	12	Deceased—10 of 12 with distant exacerbations	12	11	1			

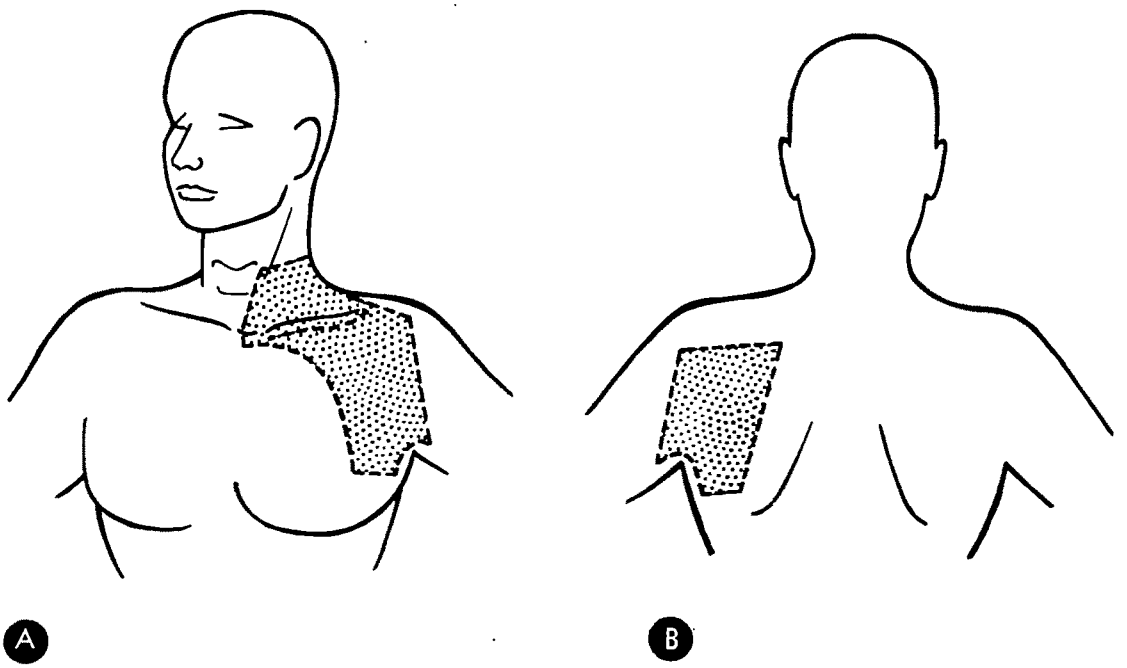


FIG. 3. (*A* and *B*) Therapy Fields for the Axilla.

(*A*) *Anterior Field.* The anterior field covers the axillary contents. The supraclavicular fossa may be included in this field prophylactically. The patient is placed in the supine position with the head rotated to the opposite side. The arm is placed at 45° angle to the body.

Borders of the supraclavicular section are as shown in the diagram. The medial border to the axillary section follows the rib cage, the inferior border follows the pectoralis major muscle, except when it is necessary for the beam to "fall off" to cover prominent nodes. The lateral border cuts across the head of the humerus.

(*B*) *Posterior Field.* The posterior field is restricted to the axilla. The patient is placed in the prone position with the head turned to the opposite side. The arm is placed at a 45° angle to the body.

The medial border follows the rib cage. It is identified by palpating the tissues between the apex of the axilla and the posterior surface of the chest wall. The lateral border follows the lattissimus dorsi muscle to cut across the head of the humerus. The superior border follows the spine of the scapula.

Given Dose (both Co^{60} and 250 kv.) to the anterior field—200 rads per day, *i.e.*, 1,000 rads per week. Prophylactic dose to the supraclavicular fossa is discontinued after 2,500 rads.

Tumor Dose to the axilla—200 rads per day, *i.e.*, 1,000 rads per week, taken at the midaxillary line.

Total Tumor Dose to the axilla—3,000 to 4,500 rads. Booster dose added for residual disease.

250 kv. unit with parallel opposed anterior and posterior fields. In 8 patients the anterior field was extended to include the supraclavicular fossa for prophylaxis (Fig. 3, *A* and *B*). The average tumor dose, administered at a rate of 750 to 1,000 rads per week was in the order of 3,000 to 4,500 rads. A booster dose, similar to the one described above for involved lymph nodes of the neck, was added for residual axillary involvement. The prophylactic dose to the supraclavicular fossa was approximately 2,500 to 3,000 rads.

Treatment results for patients with involvement of the axilla were gratifying. In all but one of the 16 cases, the disease was controlled in the local area. Ten patients are alive without new manifestations of disease, 7 for a period of more than 5 years (Table VII). Six patients who received treatment to the supraclavicular fossa are alive without new manifestations of disease.

TABLE VII

STAGE I—AXILLA

Total No. 16		Clinical Evolution		Duration (yr.)				
Treatment: 250 kv.	16			1	2–4	5	6–9	10
Local Control	15	Alive—no distant exacerbations	10	1	2	2*	4*	1
		Alive—distant exacerbations	1		1			
		Deceased—distant exacerbations	4	4				
Local Failure	1	Deceased—distant exacerbations	1				1	

* Two lost to follow-up at 60 and 87 months.

INGUINAL REGION

There were 16 cases with lymphomatous involvement of the inguinal region. The majority of these cases were treated with a 250 kv. unit, with a single anterior field. The tumor dose schedules and the final doses achieved were the same as for the axillary region. In 13 cases the disease was controlled in the local area. However, only 6 patients are alive without evidence of either local recurrence or new manifestations of disease (Table VIII). This discrepancy between the results obtained in the axilla and the results obtained in the inguinal area can be explained by the difficulty of ascertaining the status of the paraaortic lymph nodes. It is hoped that lymphangiography will aid in assessing both the iliac and the retroperitoneal regions.

ABDOMEN

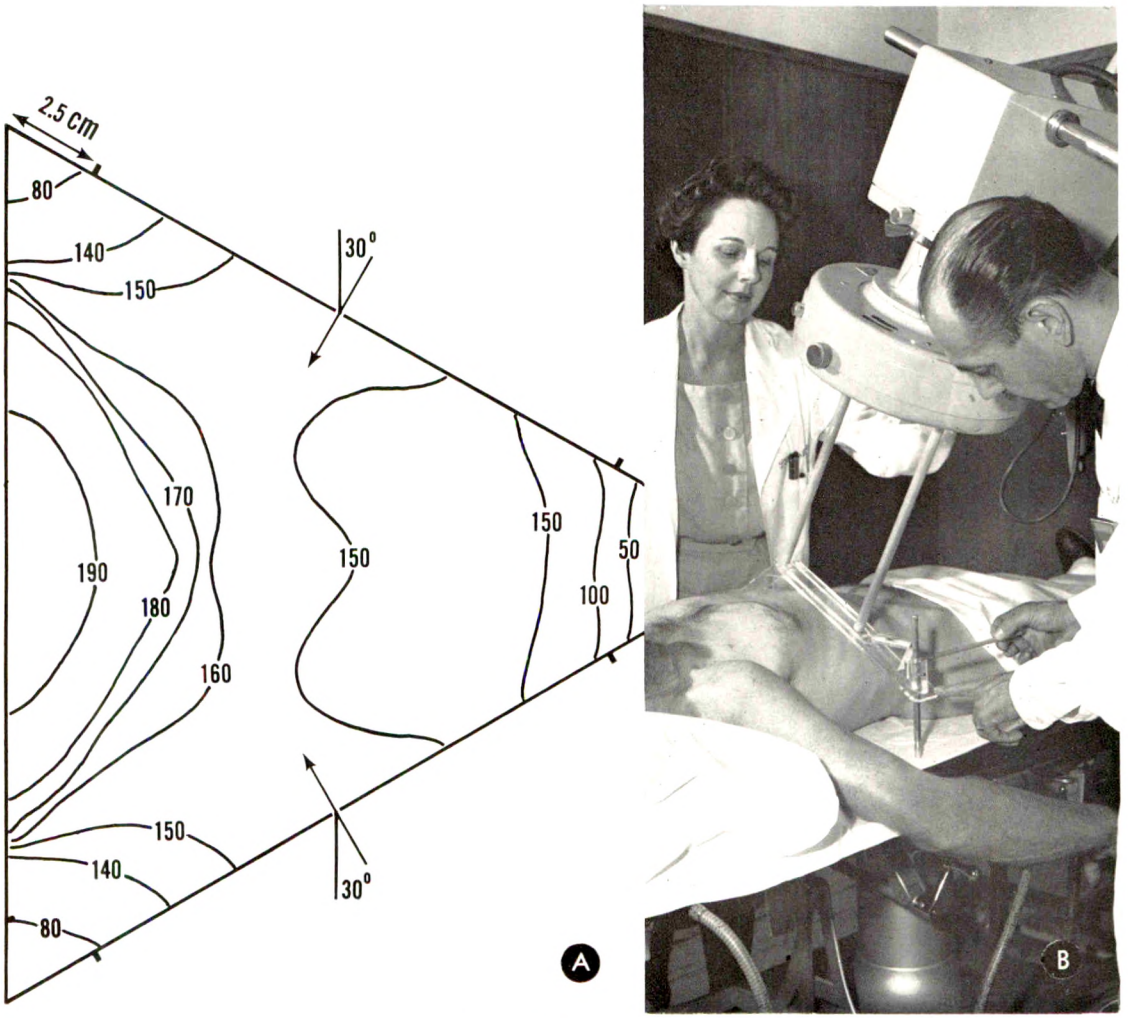
The policy of management of abdominal involvement is divided into two periods. Prior to 1955, treatment was restricted to demonstrable disease and, in deference to the systemic tolerance, both the daily dose rates and the total tumor doses were low. Because of a dissatisfaction with the results obtained, a change of policy was gradually introduced in 1955. Since that time, patients in good general condition have received radical treatment directed toward the major part of the abdomen. The techniques have been: (1) the 4 field trunk-bridge method with either orthovoltage or supervoltage therapy (Fig. 4, *A*, *B* and *C*); (2) parallel opposed fields with supervoltage therapy; or (3) the "moving strip" technique with supervoltage therapy.

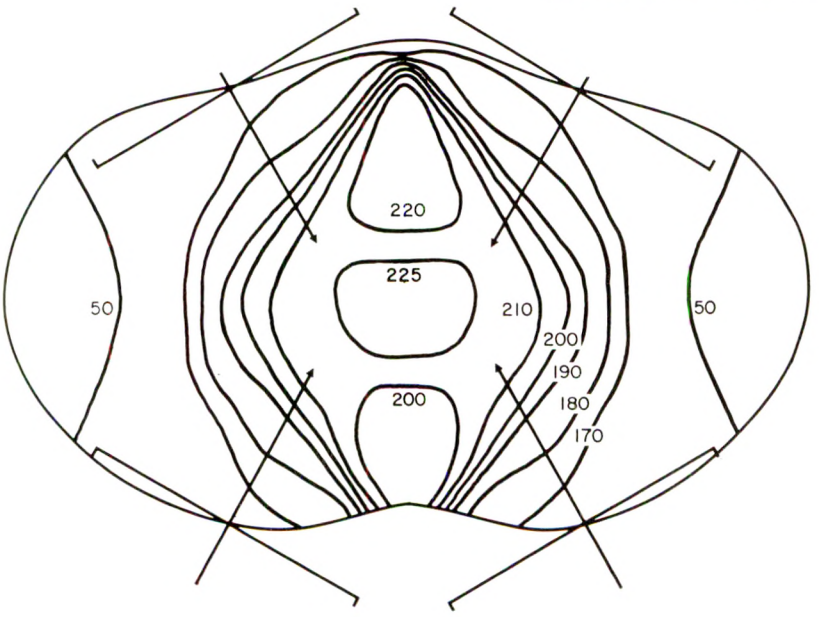
Although the isodose distribution frequently is not ideal, treatment with the trunk-bridge method is well tolerated. Depending on whether the whole abdomen is irradiated or whether the treatment is re-

TABLE VIII

STAGE I—INGUINAL AREA

Total No. 16		Clinical Evolution		Duration (yr.)				
Treatment: 250 kv.	15			1	2–4	5	6–9	10
Co^{60}	1							
Local Control	13	Alive—no distant exacerbations	6	2	2		1	1
		Alive—distant exacerbations	4	1	2		1	
		Deceased—distant exacerbations	3	1	2			
Local Failure	3	Deceased—distant exacerbations	3	2	1			


2.5 cm
80
140
150
30°
170
190
180
160
150
150
50
100
150
140
80
30°
A
B


220
225
50
210
200
190
180
170
200
50
C

stricted to the para-aortic lymph nodes, a maximum tumor dose of 750 to 1,000 rads per week generally can be tolerated, for a maximum tumor dose of 3,000 to 4,500 rads. The maximum tumor dose that can be tolerated with parallel opposed fields using the cobalt 60 unit is in the same order of magnitude, and is given at a weekly rate of 750 rads. When applicable, the "moving strip" is the best technique for treating the entire abdomen.[2] Using this technique, a tumor dose of 2,800 rads can be administered to each strip in a period of 12 days. The total time required to treat the entire abdomen is approximately 6 weeks. Because of an excessive integral dose, the "moving strip" technique is not suitable for patients over 22.0 cm. in diameter. It is contraindicated in cases with gastrointestinal bleeding, impeding obstruction, ascites, leukopenia, and thrombocytopenia. Upon completion of treatment to the entire abdomen with any of the total abdomen techniques, additional treatment for residual disease can usually be added through reduced fields. Tumor doses of 1,000 to 2,000 rads, given in 1 to 2 weeks, generally can be tolerated. However, the total dose to any given area should not exceed 5,000 rads.

Results of Treatment. The results for the group of patients treated prior to 1955 are depressing. Death, caused by local disease, occurred within the first year in 12 of 13 patients. By comparison, the results for patients given total abdominal irradiation are decidedly more encouraging. Six of 8 patients have survived for a period of 2 to 4 years without evidence of local recurrence. Two of these patients eventually died of distant manifestations of disease. Four have no evidence of local recurrence or of fresh manifestations of disease (Table IX).

MISCELLANEOUS ANATOMIC REGIONS

There were 10 cases of miscellaneous origin in the Stage I group. Specifically, the areas involved were: the retro-orbital space, the mandible, the maxilla, the ilium, the epitrochlear lymph nodes, the supraclavicular soft tissues, and the mediastinum. Radical treatment in the order of 4,000 rads in 4 weeks was administered to each of these areas. Seven of these patients are without evidence of local recurrence or new manifestations of disease.

STAGE II

In the Stage II group, the lymphomatous diseases were limited to the upper torso in 51 patients. The mediastinum was affected in 36 instances. Unilateral involvement of the lung occurred in 6 of these patients; in 4 instances the lesions were adjacent to the hilus.

Radical treatment was administered to all involved areas in 49 patients. In the majority of instances, the affected areas were treated concurrently with a tumor dose of 3,000 to 4,500 rads, delivered at a rate of 500 to 750 rads per week. On the basis of the results of treatment, we believe that a weekly tumor dose of 500 to 750 rads is not quite adequate. Our current policy is to deliver a tumor dose of 750 to 1,000 rads per week to a limited number of areas. Critical areas are treated first. These areas are usually the head and neck and/or the mediastinum.

In determining whether the head and neck and the mediastinum should be treated concurrently, or in series, the decision is based on the urgency for treatment to each area, the total volume to be irradiated, the general condition of the patient, and the availability of supervoltage time. Occasionally, because of massive involvement at the junction of the supraclavicular fossae and the mediastinum, it is necessary to treat the head and neck and the mediastinum in continuity. However, because of the obliquity of the surface between the neck and the mediastinum, it is technically

FIG. 4. (*A*) Isodose Distribution, Trunk Bridge—250 kv. Four Field Arrangement. Field Size—20×15 cm.; F.S.D.—70 cm.; H.V.L.—3.0 mm. Cu.

(*B*) Trunk Bridge Adapted to 250 kv. Unit.

(*C*) Isodose Distribution, Trunk Bridge—Co^{60}. Four field arrangement. Field Size—35×14 cm.; F.S.D.—100 cm. (FLETCHER, G. H. Therapy with ultrahard roentgen rays. In: Handbuch der medizinischen Radiologie. Chapter 8. Springer-Verlag, Heidelberg. In press. Reproduced by permission.)

TABLE IX

STAGE I—ABDOMEN

Total No. 22		Clinical Evolution		Duration (yr.)				
Treatment: 250 kv.	14			1	2–4	5	6–9	10
Co^{60}	7							
Surgery first	5							
Surgery only	1							
Local Control	9	Alive—no distant exacerbations	5	2	3			
		Alive—distant exacerbations	2		1		1*	
		Deceased—distant exacerbations	1		1			
		Deceased—other causes	1		1			
Local Failure	13	Deceased	13	12	1			

* Surgery only for lymphomatous disease limited to the stomach.
Abdominal organ involvement only—7 (gastrointestinal tract—6; liver—1).
Abdominal organ plus lymph node involvement—7.
Lymph node involvement only—8.

difficult to deliver a uniform tumor dose throughout the area.

Results of Treatment. The 5 year survival rate for the Stage II group is 51.6 per cent, the standard error being 7.79 (Table XII). This figure, which is comparable to the survival rate of the Stage I group, is supportive evidence for radical treatment in the majority of the Stage II cases. The local results, correlated with the clinical evolution, are given in Table X. Of 31 patients, in whom the disease was controlled in the local areas, 6 have lived between 6 and 10 years without evidence of local recurrence, or new manifestations of disease. Another 8 patients have survived between 2 and 4 years without evidence of disease.

STAGE III

The management of patients presenting with Stage III disease is generally directed toward the palliation of symptoms. Tumor doses are in the order of 1,000 to 2,000 rads delivered in 1 to 2 weeks.

Semiradical to radical therapy has effected worthwhile periods of remission in a small percentage of patients. In selecting patients for radical treatment, certain

TABLE X

STAGE II—CORRELATIONS OF RESULTS OF TREATMENT AND CLINICAL EVOLUTION

Total No. 53		Clinical Evolution		Duration (yr.)				
Treatment: 250 kv.	41			1	2–4	5	6–9	10
Co^{60}	12							
Local Control	31	Alive—no distant exacerbations	24	10	8		5	1
		Alive—distant exacerbations	3	1			2	
		Deceased—distant exacerbations	4	3		1		
Local Failure	20	Alive—distant exacerbations	3	1		1	1	
		Deceased—distant exacerbations	17	10	5	2		
Deceased—no follow-up	2							

TABLE XI

COMPARISON OF STAGE III SURVIVORS

Total No. Living—19	No.	Treatment with Emphasis on Chemotherapy	Treatment with Emphasis on Roentgen Therapy	Semiradical to Radical Roentgen Therapy	Duration (yr.)				
					1	2–4	5	6–9	10
Group I Abdomen, mediastinum and periphery	4	1	3	3	2	2			
Group II Abdomen and periphery	10	2	8	7	3	6	1		
Group III Mediastinum and periphery	0								
Group IV Periphery	5	0	5	2		1	2	1	1
Total No. Deceased—75									
Under 2 years	55								
2–4 years	16								
5–9 years	4								

criteria are of value, such as: satisfactory general condition, chronic history, absence of hematologic abnormalities, etc. Tumor dose levels are dependent upon the volumes of tissue involved. Radical treatment, with tumor doses in the order of 3,000 rads, if given in series, can usually be delivered to all the peripheral lymph node bearing areas, in addition to either the mediastinum or the abdomen. Hematologic values are better maintained if the major area, *i.e.*, the abdomen or the mediastinum, is treated first.

For involvement of the two major lymph node bearing areas, the mediastinum and the abdomen, together with the peripheral lymph node bearing areas, it may be possible to administer tumor doses in the order of 2,000 rads to each area, provided that the treatment can be given in series. Hematologic values are better maintained if the abdomen is treated first.

Results of Treatment. The majority of the 75 patients treated with palliative intent were deceased within the first year. For comparative purposes, the 19 living patients have been divided into 4 groups according to the initial involvement (Table XI). Although the numbers are small, it is of interest that, in the survivors, there were no cases with involvement of the mediastinum and the peripheral lymph node bearing areas. From the results obtained for the groups with either peripheral lymph node involvement or peripheral lymph node and abdominal involvement, it would seem that radical treatment should be given to all such patients in good general condition presenting with Stage III disease. Finally, although it is not possible to administer radical treatment to patients with abdominal, mediastinal, and peripheral lymph node involvement, it is occasionally worthwhile to administer semiradical treatment to all the involved areas.

DISCUSSION

Control of the local manifestations of the lymphomatous diseases was obtained in the majority of the patients with Stage I or Stage II involvement who received radical

TABLE XII

SURVIVAL TABLE (MODIFIED LIFE METHOD)

Years	Alive at Beginning of Interval	Died During Interval	Lost to Follow-up During Interval	Withdrawn Alive During Interval	Cumulative Per Cent Survival	Standard Error
All Stage I						
1	131	28	—	—	78.6	3.61
3	64	6	—	7	55.1	4.61
5	35	1	—	11	47.3	4.94
Stage I—Head and Neck						
1	67	16	—	—	76.1	5.22
3	30	1	—	4	54.5	6.33
5	16	—	—	7	44.8	6.81
Stage II						
1	53	10	—	—	81.1	5.39
3	27	4	—	3	57.6	7.42
5	16	—	—	2	51.6	7.79
Stage III						
1	94	43	—	—	54.3	5.15
3	34	11	—	2	27.3	4.80
5	14	1	—	4	19.9	4.52
All Stages						
1	278	81	—	—	70.9	2.72
3	125	21	—	12	45.8	3.16
5	65	2	—	17	38.4	3.26

radiation therapy. Entire regions rather than areas of palpable disease were treated intensively to avoid marginal recurrences. Total tumor doses of 3,000 to 4,500 rads were given. A booster dose was added when indicated for residual disease. A tumor dose rate of 750 to 1,000 rads per week is recommended. Local recurrences are more frequent when the tumor dose rate is less than 750 rads per week. The results of radical treatment to the major part of the abdomen for Stage I disease are encouraging, despite the rather short follow-up period. Supervoltage is recommended for involvement of Waldeyer's ring, the mediastinum in heavy-set individuals, and the entire abdomen, when the "moving strip" technique is indicated.

In reviewing the local results of treatment in the Stage I and Stage II groups in relation to the clinical evolution, it appears that a remission of at least 1 year, and generally several years, occurred in the majority of the cases in which the disease had been controlled locally. Similarly, it appears that the patients who received prophylactic treatment to the surrounding areas tended to have longer periods of remission. In the cases in which the disease was not controlled locally, the over-all life expectancy tended to be poor.

Although the results of treatment for the Stage III group are unpredictable, it appears that semiradical to radical treatment is of value in selected cases.

SUMMARY

Two hundred and seventy-eight cases with lymphomatous diseases have been reviewed. The results of treatment have been presented by stage and region. Radical treatment to the areas of involvement is of value in the Stage I and the Stage II cases from the standpoint of local control and duration of remissions. Similarly, prophylactic treatment also appears to be of value in the Stage I and Stage II cases. Semiradical to radical therapy is of value in a small percentage of Stage III cases. In biologically aggressive lymphomas, which generalize rapidly, failure to control the local lesion is apt to occur despite radical treatment.

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THE ENLARGED THYMUS GLAND IN LEUKEMIA IN CHILDHOOD*

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LEUKEMIA is the commonest malignancy in childhood, accounting for about one-third of all malignancies in those below the age of 15 years. Its mode of onset is protean, and may simulate many other diseases before its true nature is discovered.

Though its ultimate prognosis still is hopeless, the use of chemotherapeutic agents has lengthened the survival time in leukemia. Because of this prolonged time, many organs not usually involved in the disease process now are invaded, and it is not unusual to find such organs as the testes, the meninges, and the heart infiltrated with leukemic tissue at autopsy.

The onset, course, and development of childhood leukemia is different in many respects from this disease in adult life, and this is particularly true in the organs involved. Mediastinal lymph node involvement has been an infrequent finding on the chest roentgenograms of our patients with leukemia.[3,4] However, marked infiltration of the thymus gland has been encountered in several instances, and its roentgen apperance seems to be highly suggestive of leukemia. This appears as a flat sheet of tissue in the anterior mediastinum, with its lower margins frequently merging with that of the heart. The great vessels are hidden beneath this leukemic tissue.[1] This infiltration has appeared in several patients with known leukemia and previously normal chest roentgenograms. When the patient enters a period of remission (following treatment or spontaneously), the thymic infiltration resolves. In many of our cases, the degree of thymic infiltration apparently parallels the size, clinically evaluated, of the liver and spleen. All of the patients in our series received some form of adrenocorticosteroid therapy after the diagnosis had been made, and this may well be associated with the shrinkage.[2]

In several patients, admitted for diagnostic work-up, the appearance of the chest roentgenogram has been sufficient to suggest a bone marrow examination. In one case, the presenting complaint was bilateral abdominal masses which later proved to be leukemic renal masses. The chest roentgenogram demonstrated a large leukemic infiltrate.

Histopathologically, a leukemic lymph node is similar in appearance to that of an isolated lymphosarcoma, and examination of the bone marrow is necessary. In lymphosarcoma, the latter is normal until the advanced stages. The relationship of these two malignancies is in question, and lymphosarcoma isolated to the lymph nodes may be but a stage of generalized lymphoma (leukemia). In one patient, the diagnosis of lymphosarcoma had been made from biopsy of a cervical lymph node, and at this time the bone marrow had been normal. The progression to leukemia was suggested by the later appearance of thymic infiltration on a routine chest roentgenogram. The bone marrow was then leukemic.

ILLUSTRATIVE CASES

CASE 1. G.T., 2 year, 7 month old male (C.H. #67524). This patient was seen for swelling of the lymph nodes in the left supraclavicular area. The liver was enlarged. A biopsy of one lymph node showed lymphoma. The bone marrow study and chest examination were normal (Fig. 1*A*). The white blood cell count was 5,700. The patient received radiation therapy with resultant regression of the enlarged lymph

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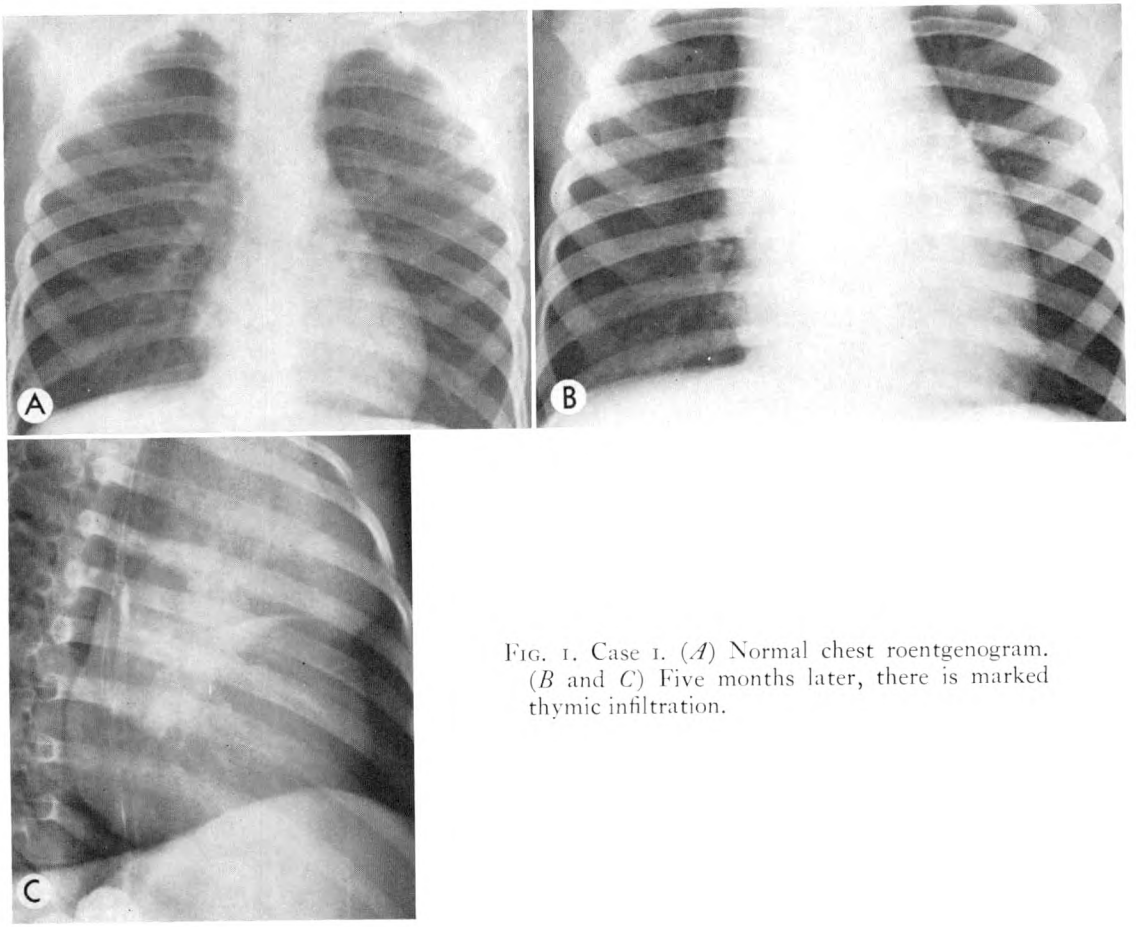


Fig. 1. Case I. (*A*) Normal chest roentgenogram. (*B* and *C*) Five months later, there is marked thymic infiltration.

nodes. On routine chest roentgenograms 5 months later (Fig. 1, *B* and *C*), a large thymic infiltration was present. At this time the bone marrow showed acute leukemia.

Case II. K.B., $9\frac{1}{2}$ year old female (C.H. #59180). Classical leukemia. On a chest roentgenogram (Fig. 2*A*) there was a marked thymic infiltration. The liver and spleen were also found to be enlarged. The white blood cell count was 53,000. Following therapy with steroids, the chest roentgenogram (Fig. 2*B*) 2 months later was nearly normal. The patient died soon thereafter.

Case III. W.B., 6 year old male (C.H. #49142). This patient had leukemia with cervical and inguinal lymphadenopathy. The white blood cell count was 10,750. The thymus was found to be enlarged on a chest roentgenogram (Fig. 3*A*). Four months later, the chest roentgenograms (Fig. 3, *B* and *C*) were normal, and remission of the process was noted.

Case IV. G.F., 5 year old male (C.H. #37672). This patient was referred because of bilaterally enlarged, palpable kidneys. A chest roentgenogram (Fig. 4*A*) showed thymic infiltration. Acute leukemia was diagnosed on marrow aspiration. An excretory urogram was compatible with leukemic infiltration of the kidneys. After 10 days of steroid therapy, the kidney masses had resolved considerably. A chest roentgenogram at this time (Fig. 4*B*) was normal.

Case V. F.B., 18 month old female (C.H. #65365). This patient was admitted because of a red, inflamed eye. Biopsy of a retro-orbital mass showed lymphoma. The bone marrow examination was normal. A chest roentgenogram was also normal (Fig. 5*A*). Two and one-half months later, a chest roentgenogram showed the thymus as well as the heart to be enlarged (Fig. 5*B*). The bone marrow study revealed acute leukemia. At postmortem examination there was

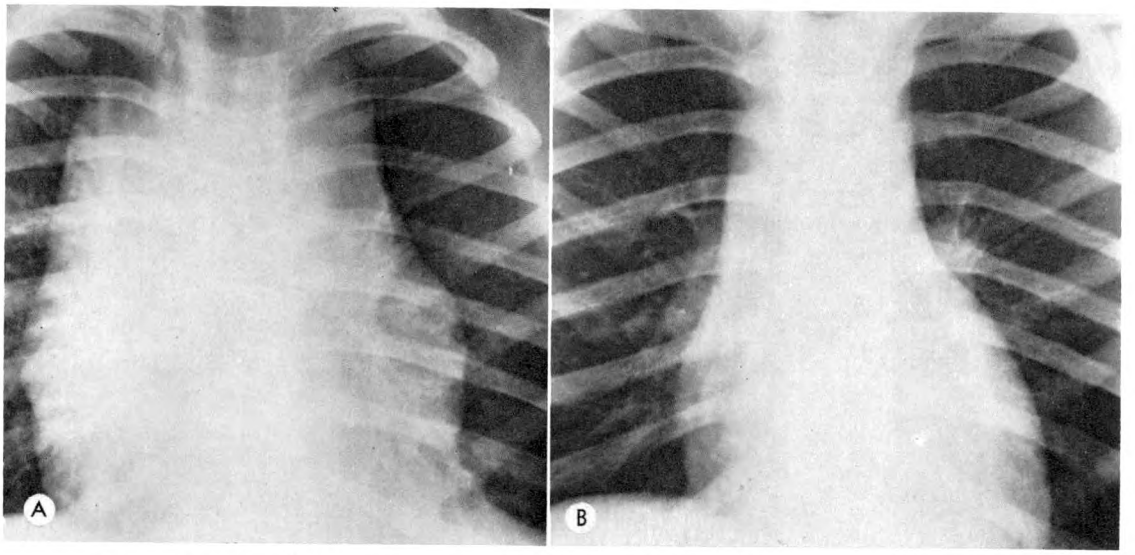


FIG. 2. Case II. (*A*) Roentgenogram shows marked thymic infiltration. (*B*) Two months later, the chest is nearly normal, with resolution of the infiltration.

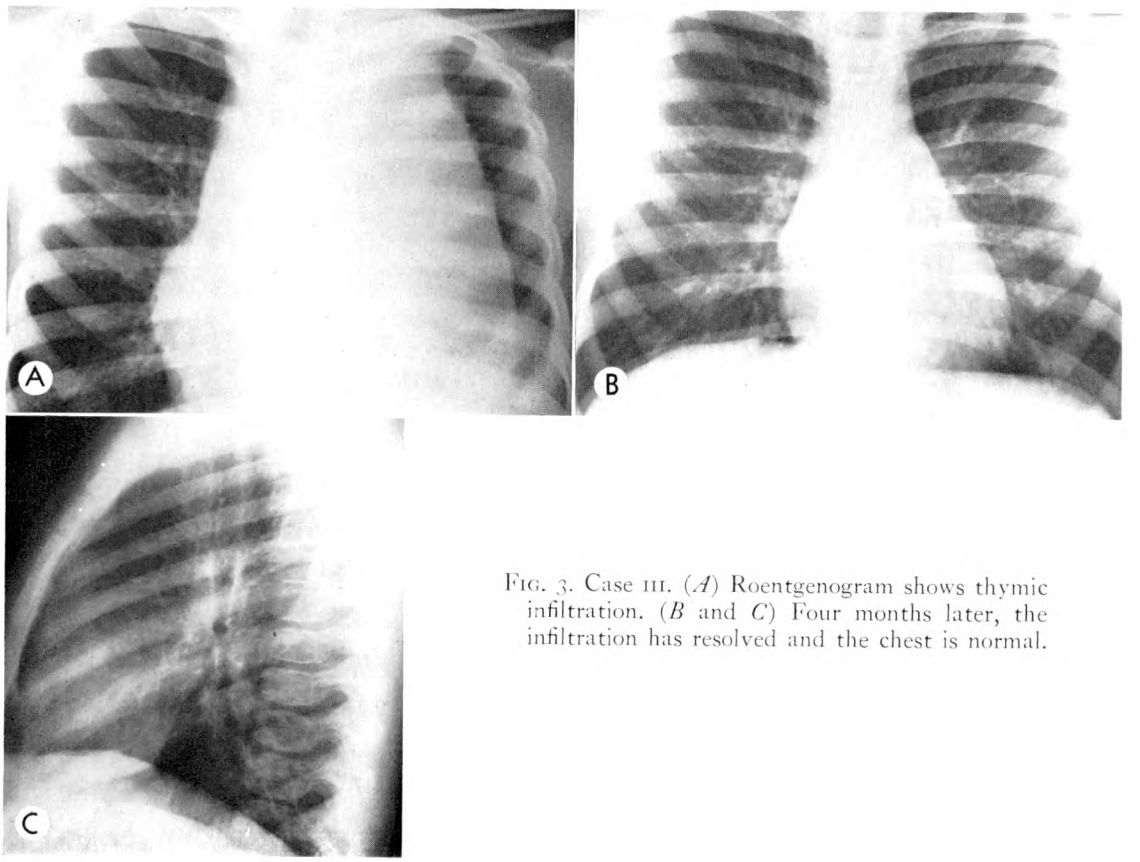


FIG. 3. Case III. (*A*) Roentgenogram shows thymic infiltration. (*B* and *C*) Four months later, the infiltration has resolved and the chest is normal.

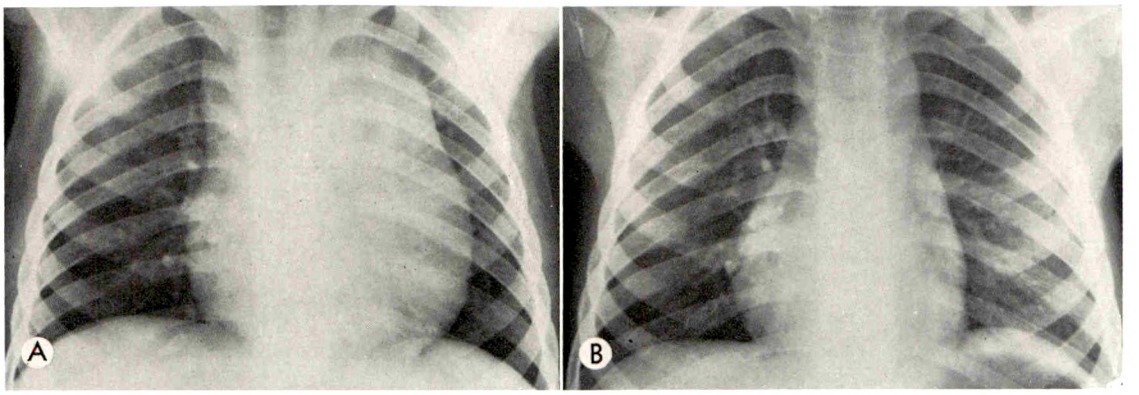


FIG. 4. Case IV. (*A*) Roentgenogram shows a sheet-like thymic infiltration. (*B*) Ten days later, the infiltration has resolved.

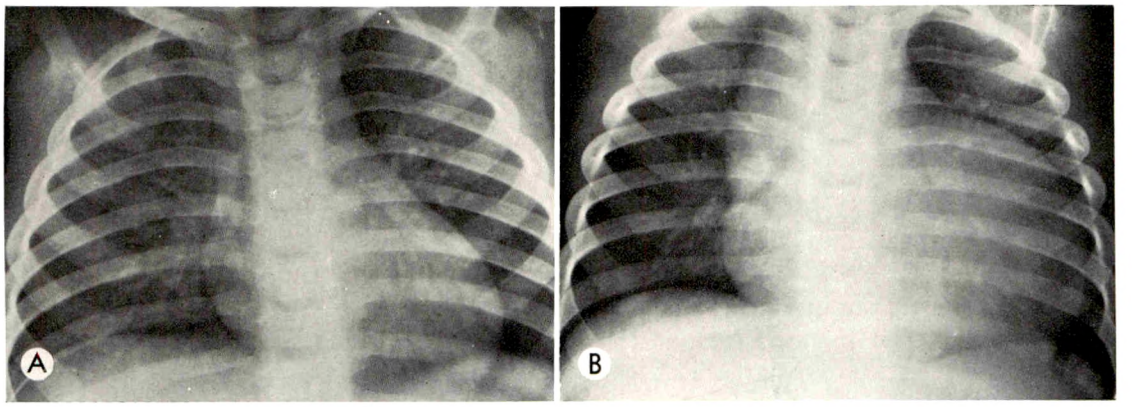


FIG. 5. Case V. (*A*) Roentgenogram shows normal chest. (*B*) Two and one-half months later, the thymus gland is infiltrated and the heart is enlarged.

leukemic infiltration in the thymus gland and the myocardium.

CONCLUSION

1. The thymus gland frequently becomes enlarged in children with leukemia, and this appearance on a chest roentgenogram may be an important clue to diagnosis.

2. The roentgenologic regression of this gland following chemotherapy (steroids?) roughly parallels the clinical remission.

3. These findings show an interesting relationship of the thymus gland to childhood leukemia.[5,6]

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RENAL INVOLVEMENT IN LYMPHOMAS AND LEUKEMIAS IN ADULTS*

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THE renal manifestations of lymphoma and leukemia have been evaluated from the clinical course of the patient or studies made of surgical specimens and postmortem material. However, the roentgen manifestations of renal involvement by this type of neoplastic disease in the adult have not been as fully described and recorded. Our objective in this review of 20 confirmed cases of renal lymphoma or leukemia is to establish roentgen criteria for the correct interpretation of this type of involvement.

HISTORICAL REVIEW

PATHOLOGIC ASPECTS

The original report of lymphosarcoma of the kidneys was made by Turner in 1878.[1] As of 1950, Allen, Berg and Rosenblatt[1] recorded the nineteenth case of renal lymphosarcoma which was found in a 41 year old white male. An intravenous pyelogram showed bilateral enlargement of the kidneys and changes similar to polycystic disease. At autopsy the kidneys were greatly enlarged with diffuse microscopic infiltration of the parenchyma.

A case of lymphosarcoma of the kidneys, adrenal glands, and perirenal adipose tissues in a 67 year old white male was reported by Davis and Olivetti.[7] The intravenous pyelogram showed poor function on the right and no function on the left. The clinical manifestations included anemia, hematuria, and progressive renal failure. At autopsy the kidney cortex was diffusely infiltrated, while the medulla was relatively uninvolved.

Baldridge and Awe,[2] in a study of 39 cases of lymphoma, observed microscopic kidney involvement to be present in 20 cases. Chute[6] reported the pathologic results in 5 patients with lymphoma of the kidney. In 2 of these there was diffuse infiltration of the kidneys; in one, multiple nodules were present. When hematuria occurred, it was usually painless. Infection and urinary tract obstruction were frequently present. Barney, Hunter and Mintz[3] reported 39 cases of lymphoma and lymphatic leukemia with clinical manifestations of urinary tract involvement. Almost 60 per cent of the patients showed gross or microscopic involvement of the urinary tract.

Merrill and Jackson[13] stressed the frequent incidence of renal failure in adults in cases of leukemia or lymphoma. The causes of renal failure included diffuse kidney infiltration by the neoplastic process, ureteral obstruction by retroperitoneal masses, and "degenerative" lesions of the kidneys. Kirshbaum and Preuss[11] in reporting 123 cases of leukemia pointed out that the kidney is the most frequently involved organ in all forms of leukemia. These authors stressed that the usual involvement was by infiltrates of myeloid or lymphoid cells into the glomerular tufts or the interstitial connective tissue. Less commonly, infiltrates were present in the renal capsule and in the perirenal fat. Meyer[14] described 3 forms of renal involvement by leukemia and lymphoma: (1) nodular; (2) diffuse infiltration; and (3) masses at the hilus causing pelvic obstruction (an infrequent finding).

Gibson[9] quotes Puente Duany on lymphosarcoma of the kidney. He described 4

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different types: (1) a capsular type in which the kidney was engulfed from without by a mass (perirenal type of involvement); (2) bilateral diffuse lymphosarcoma infiltration with uniform enlargement of the organ most marked in the cortex and usually seen in infants (relatively rare); (3) nodular type (most frequent); and (4) a large solitary tumor.

Watson, Sauer, and Sadugor[15] studied 1,073 cases of lymphoblastoma admitted to the Roswell Park Hospital of which 456 were lymphosarcoma, 234 leukemia, and 383 Hodgkin's disease. Of this group, 7.5 per cent (80 cases) had various degrees of urinary tract involvement clinically. The incidence of urinary tract involvement in these 3 categories was as follows: leukemia—13.6 per cent; lymphosarcoma—9.5 per cent; and Hodgkin's disease—1.3 per cent. Hematuria was a common finding. The kidneys were the most frequently involved portion of the urinary tract (82.5 per cent). In the 143 autopsied cases, urinary manifestations were present in almost one-half. Actual pathologic involvement of the urinary tract was found in 58.6 per cent of those with leukemia; 61.9 per cent with lymphosarcoma; and 6.6 per cent with Hodgkin's disease.

In this series the kidney was affected in the following ways: (1) renal displacement by an enlarged spleen or enlarged retroperitoneal lymph nodes; (2) neoplastic invasion of the kidney by direct extension; and (3) involvement of the renal parenchyma by multiple microscopic nodules. The latter represented the commonest type of involvement. The more extensive the infiltration, the greater was the impairment of renal function. Microscopic involvement was noted in 25 cases (7 lymphosarcoma and 18 leukemia). Three patterns predominated: (1) diffuse infiltration of the intertubular connective tissue; (2) involvement of periglomerular structures; and (3) invasion of the perivascular spaces. In leukemia, therefore, the renal involvement is apparent more often microscopically than grossly. Dilatation of the pelvis and calyces caused by pelvic masses and ureteral obstruction was seen in several cases (2 in leukemia and 1 in Hodgkin's disease). Direct invasion of the kidney parenchyma by retroperitoneal masses occurred in one case of lymphosarcoma.

Boyd[5] reported that renal involvement by lymphoma may occur as intrinsic metastases, direct invasion or by displacement by overlying organs or enlarged lymph nodes. He noted the frequent paucity of urinary symptoms and that when present, the most significant symptoms were hematuria and pain. Hematuria is most common in the lymphatic leukemia. He indicated that the kidney was the most frequently involved portion of the urinary tract.

Klinger[12] reviewed 5,000 autopsies with secondary malignant involvement of the genitourinary tract. This type of involvement occurred most frequently with lymphoma and leukemia. There were 47 cases in which the genitourinary tract was affected by lymphoma as compared with 19 cases of metastases from lung cancer. Although other metastatic neoplasms of the kidneys may be either unilateral or bilateral, all the lymphomas involving the kidneys in this series were bilateral. The distribution was as follows: kidney 45, bladder 9, prostate gland 4, seminal vesicles 3, and testes 1. In this group of 45 patients with renal lymphoma, the most frequent clinical manifestations included albuminuria 19, pyuria 16, hematuria 6, and decreased renal function 10.

Gowdy and Neuhauser[10] recorded their observations on leukemic infiltration of the kidneys in children. They observed that leukemia causes nodular and diffuse infiltration of the cortex with hardly any involvement of the medulla. These changes were found most commonly in children but did occur in adults. Diffuse leukemia of the kidneys will show pathologically: (1) kidney enlargement, often 3–4 times normal size; (2) loss of the distinct corticomedullary junction; and (3) wide separation of the nephrons by massive cellular infiltration. The infiltration predominates in the

cortex and decreases in degree as one reaches the pelvis. The tubules are compressed and separated. Tubular and glomerular degeneration is often present.

ROENTGENOLOGIC ASPECTS

Bell, Heublein, and Hammer[4] reported that lymphosarcoma or Hodgkin's disease of the urinary tract may be diagnosed by displacement of the kidney, obstructive uropathy and pressure defects within the collecting system. Leukemia will cause invasion of the renal parenchyma.[11] The kidneys are enlarged with deformity of the pelvis and calyces; the enlargement may be due to congestive changes or infiltration or perhaps a combination of both.

Freifield,[8] reporting a case of lymphoblastoma of the kidneys, stressed that bilaterally enlarged kidneys and azotemia with an intravenous pyelogram suggesting polycystic kidneys may indicate the presence of lymphoma.

According to Gowdy and Neuhauser,[10] the significant findings on roentgenograms include: (1) bilateral moderate or marked symmetric kidney enlargement; (2) enlargement of the renal pelvis without dilatation or evidence of obstruction; (3) calyceal and infundibular elongation without renal deformity; and (4) filling defects in the collecting system, and displacement and irregularity of the renal outline. All 3 cases reported by these authors gave prompt excretion on excretory urography. One case showed a decrease in kidney size following radiation therapy.

Gibson[9] reported 3 cases of lymphosarcoma in adult males. These cases fell into 3 categories: (1) initial symptoms were related to constriction of the ureters by retroperitoneal masses; (2) the simulation of a renal carcinoma on intravenous pyelograms by the lymphomatous involvement; and (3) obvious retroperitoneal masses with secondary renal invasion.

The roentgen findings of renal lymphosarcoma on excretory urography therefore are as follows: (1) delayed or poor opacification; (2) symmetric enlargement of the renal densities with normal retroperitoneal tissues; (3) considerable elongation and slight enlargement of the calyces and infundibula; (4) increase in the renal cortical thickness averaging 5.8 cm.; (5) absence of caliectasia; (6) sharp definition of the psoas margins; and (7) findings simulating polycystic disease but without real calyceal deformities, filling defect, displacements or irregularities. These changes are much the same as those described by Gowdy and Neuhauser[10] in leukemia in children except for better and more prompt opacification on excretory urography in the leukemia group than in the lymphoma patients.

CLINICAL MATERIAL

We are presenting a series of 20 patients with renal involvement by lymphoma or leukemia (histologically verified) on whom excretory urography was performed. There was no significant sex predilection with 11 males and 9 females. The age distribution was from 27 to 72 years (Table I). Three-fourths of the cases occurred in the 51–80 year group. This group included the 4 patients with lymphatic leukemia. Histologically, there were 16 patients with malignant lymphoma and 4 with lymphatic leukemia (Table II).

In 3 cases (all lymphosarcoma) the initial presenting lesion was renal and localized to the kidney. However, at postmortem study all patients demonstrated other sites of tumor involvement.

The findings on physical examination in the entire series with lymphoma or leukemia of the kidney are summarized in Table III. Hepatomegaly was most frequently observed (15 patients). Splenomegaly was present in 12 cases. In 9 instances a mass in the renal area was encountered, and in 6 patients there was pain or tenderness in the kidney region.

A summary of the significant laboratory findings is presented in Table IV. Eleven patients showed evidence of hematuria, 2 gross and 9 microscopic. In several instances this hematuria was found in the terminal stage of the disease. Urinary tract

TABLE I

AGE DISTRIBUTION

Age	No. of Patients	Lympho-sarcoma	Reticulum Cell Sarcoma	Hodgkin's Disease	Lymphatic Leukemia
21–30	2	0	2	0	0
31–40	1	1	0	0	0
41–50	2	1	0	1	0
51–60	4	1	1	1	1
61–70	8	4	1	2	1
71–80	3	1	0	0	2
Total	20				

TABLE II

MICROSCOPIC DIAGNOSIS

Malignant Lymphoma		16
Lymphosarcoma	8	
Hodgkin's Disease	4	
Reticulum Cell Sarcoma	4	
Lymphatic Leukemia		4
Total		20

TABLE III

FINDINGS ON PHYSICAL EXAMINATION

Diagnosis	Hepato-megaly	Spleno-megaly	Mass in Renal Area	Pain or Tender-ness in Renal Area
Lymphosarcoma	6	3	7	3
Hodgkin's Disease	2	2	0	1
Reticulum Cell Sarcoma	3	3	2	1
Lymphatic Leukemia	4	4	0	1
Total	15	12	9	6

TABLE IV

SIGNIFICANT LABORATORY DATA

Hematuria		11
Gross	2	
Microscopic	9	
Albuminuria		11
Pyuria		10
Blood Urea Nitrogen above 25 mg.		7
Nephrotic Syndrome		2
Oliguria		2

TABLE V

TIME INTERVAL FROM MICROSCOPIC DIAGNOSIS TO ROENTGEN DETECTION OF RENAL INVOLVEMENT

Less than 1 year	13
1–5 Years	3
6–10 Years	2
11–15 Years	1
16–20 Years	1

bleeding also tended to increase as the disease progressed. Albuminuria was observed in 11 cases and became more marked with the advance of the disease. Other findings included pyuria in 10 and an elevation of the blood urea nitrogen above 20 mg. in 7 patients. A progressive increase in the blood urea nitrogen then occurred as the disease advanced. In 2 patients a nephrotic syndrome was seen with edema of the lower extremities and albuminuria.

There was considerable variation of the time interval from the first histologic diagnosis of leukemia or lymphoma to the detection of renal involvement as determined by the roentgen examination (Table v). The longest interval was 18 years. Twelve of the 19 patients showed evidence of renal involvement within 1 year after the histologic diagnosis had been first established. By contrast, the time interval from the roentgen diagnosis of renal lymphoma or

TABLE VI

TIME INTERVAL FROM ROENTGEN DETECTION OF RENAL INVOLVEMENT TO DEATH OF PATIENT

Less than 4 months	14
5–8 Months	5
9–12 Months	1

leukemia to the death of the patient was with one exception less than 9 months (Table VI).

The roentgen evaluation of the kidneys was determined with plain roentgenograms of the abdomen followed by excretory urography. Such examinations were performed one or more times shortly before histologic studies of the kidney were obtained at surgery or postmortem study. The plain roentgenogram of the abdomen was examined for the size, shape, and position of each kidney. The soft tissue structures that were evaluated included the liver, spleen, perirenal area, and psoas muscles. The results of these observations are shown in Table VII. Localized and generalized kidney enlargement was observed in 12 cases. Localized kidney enlargement was seen in 6 cases but was found only once in the 4 leukemia patients. Five cases were seen with displacement of the kidney, and the same number had a perirenal mass. Splenomegaly was diagnosed in 11 instances in contrast to only 4 patients thought to have hepatomegaly.

A gross evaluation of renal function, as determined by the intravenous urogram, showed 7 patients with decreased renal function as evidenced by the poor visualization of the collecting system. In 5 of these cases the decreased function was unilateral, while bilateral decreased function was seen in 2 instances (Table VIII).

TABLE VIII

FINDINGS ON THE INTRAVENOUS UROGRAM

	Increased Cortical Thickness	Deformed Collecting System	Decreased Renal Excretion
Lymphosarcoma	3	5	3
Hodgkin's Disease	1	1	3
Reticulum Cell Sarcoma	2	4	0
Lymphatic Leukemia	3	3	1
Total	9	13	7

On excretory urography the collecting systems of the kidneys presented two types of abnormalities. In one group consisting of 9 cases there was an increase in the cortical thickness. In the other group there was a localized or generalized distortion of the collecting system, indicating an expanding or infiltrating process. This distortion of the system was seen in 13 instances. These findings are summarized in Table VIII.

Four roentgenographic patterns (Table IX) could be observed when the changes in the renal collecting system were studied: (1) diffuse infiltration—compression, distor-

TABLE VII

FINDINGS ON THE PLAIN ROENTGENOGRAMS OF THE ABDOMEN

Diagnosis	Enlarged Kidney	Localized Kidney Enlargement	Generalized Kidney Enlargement	Displaced Kidney	Perirenal Mass	Hepatomegaly	Splenomegaly
Lymphosarcoma	7	4	3	3	3	2	3
Hodgkin's Disease	2	1	1	1	1	1	3
Reticulum Cell Sarcoma	1	0	1	1	1	0	2
Lymphatic Leukemia	2	1	1	0	0	1	3
Total	12	6	6	5	5	4	11

Table IX

PATTERNS OBSERVED ON INTRAVENOUS UROGRAM IN CASES OF DEFORMED COLLECTING SYSTEM*

	Diffuse Infiltration	Single Nodule	Multiple Nodules	Secondary Invasion
Lymphosarcoma	4	0	4	1
Hodgkin's Disease	4	0	0	1
Reticulum Cell Sarcoma	4	1	1	0
Lymphatic Leukemia	4	0	0	0
Total	16	1	5	2

* Four patients had combined patterns of deformity of the collecting system.

tion and elongation of the calyces; (2) single nodule—displacement and deformity of the collecting system, indicating a single expanding lesion; (3) multiple nodules—multiple sites of displacement and deformity of the collecting system; and (4) secondary invasion—pressure defects of the renal pelvis with contiguity of renal and perirenal involvement.

Figures 1 through 13 are examples of the renal manifestations of lymphoma and leukemia observed in this series.

The findings on intravenous urography were correlated with the gross postmortem examination. This permitted a division into 3 categories as indicated in Table x. Three of the 4 patients with leukemia had bilateral abnormal pyelographic findings corresponding to bilateral renal abnormalities at postmortem examination. One patient with leukemia had evidence of only a unilateral pyelographic abnormality, but bilateral involvement was seen at postmortem examination.

As an aside we have attempted to evaluate the presence or absence of an enlarged liver and spleen, correlating both the physical examination and the roentgen interpretation with the postmortem studies. It was arbitrarily decided that a liver and spleen exceeding 2,000 and 300 gm., respectively, were likely to be detected as enlarged both by physical and roentgen

Table X

CORRELATION OF PYELOGRAPHIC FINDINGS WITH POSTMORTEM EXAMINATION*

	IVP—Unilateral PM—Unilateral	IVP—Unilateral PM—Bilateral	IVP—Bilateral PM—Bilateral
Lymphosarcoma	2	2	4
Hodgkin's Disease	2	0	2
Reticulum Cell Sarcoma	0	0	3
Lymphatic Leukemia		1	3
Total	4	3	12

* Postmortem examination was not performed in 1 case.
IVP = Intravenous pyelogram.
PM = Postmortem examination.

examination. The results are shown in Table xi. In estimating liver size both techniques resulted in the correct diagnosis in 12 cases. The physical examination presented 7 false positives and no false negatives. By contrast, the roentgenographic interpretations disclosed 2 false positives and 5 false negatives.

As for the splenic evaluation, both techniques gave a comparable level of accuracy. Physical examination brought forth 3 false positives and 1 false negative. The roentgen interpretation resulted in 3 false positives and 2 false negatives.

Table XI

DETERMINATION OF ENLARGED LIVER AND SPLEEN*

	Correct Diagnosis	False Negative	False Positive
	Liver		
Physical Examination	12	0	7
Roentgenography	12	5	2
	Spleen		
Physical Examination	15	1	3
Roentgenography	14	2	3

* Postmortem examination was not performed in 1 case.
The spleen was considered significantly enlarged above 300 gm., the liver above 2,000 gm.

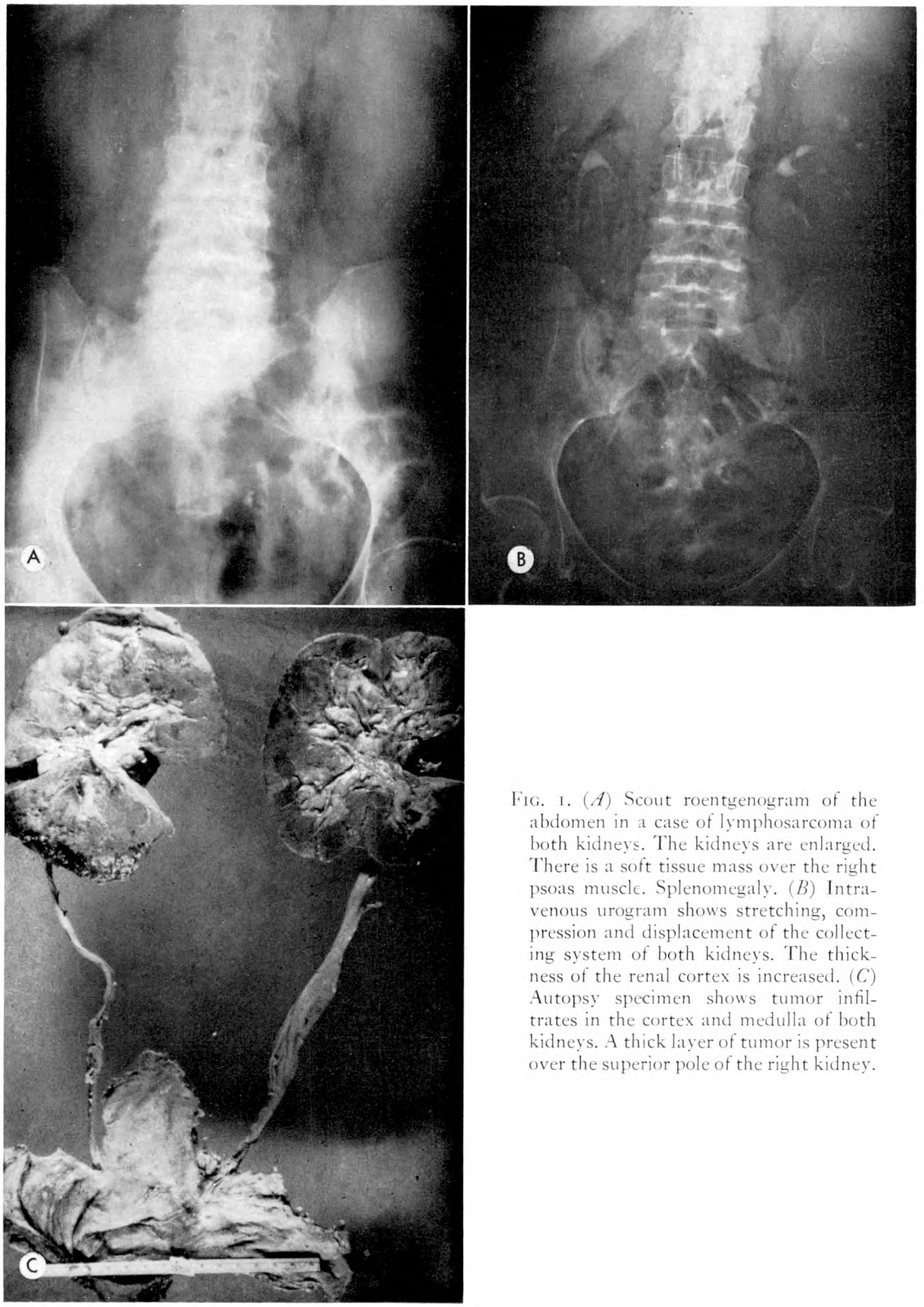


FIG. 1. (*A*) Scout roentgenogram of the abdomen in a case of lymphosarcoma of both kidneys. The kidneys are enlarged. There is a soft tissue mass over the right psoas muscle. Splenomegaly. (*B*) Intravenous urogram shows stretching, compression and displacement of the collecting system of both kidneys. The thickness of the renal cortex is increased. (*C*) Autopsy specimen shows tumor infiltrates in the cortex and medulla of both kidneys. A thick layer of tumor is present over the superior pole of the right kidney.

Several different types of treatment were used during the course of the disease in this series of patients. Ten patients received radiation therapy to the renal region. All showed a decrease in the size of the abdominal masses. One patient with oliguria and ascites received 600 r to the kidney area. This was followed by slight but temporary improvement of renal function with the patient dying 5 days after this treatment.

Other patients received cortisone, nitrogen mustard, and alkylating agents with no significant response.

DISCUSSION

In this series of 20 patients with lymphoma or leukemia of the kidney, the most frequent lesion was a malignant lymphoma. Lymphosarcoma was the microscopic diagnosis in one half of the malignant lymphomas. Although the age range for the malignant lymphoma group varied from 21 to 80, all of the lymphatic leukemia cases occurred in the group from 61 to 80 years of age. Reticulum cell sarcoma occurred in younger patients, and although lymphosarcoma was seen in younger individuals, most of the patients were in an older age group.

The significant finding on physical examination was hepatosplenomegaly. This was encountered in all 4 patients with leu-

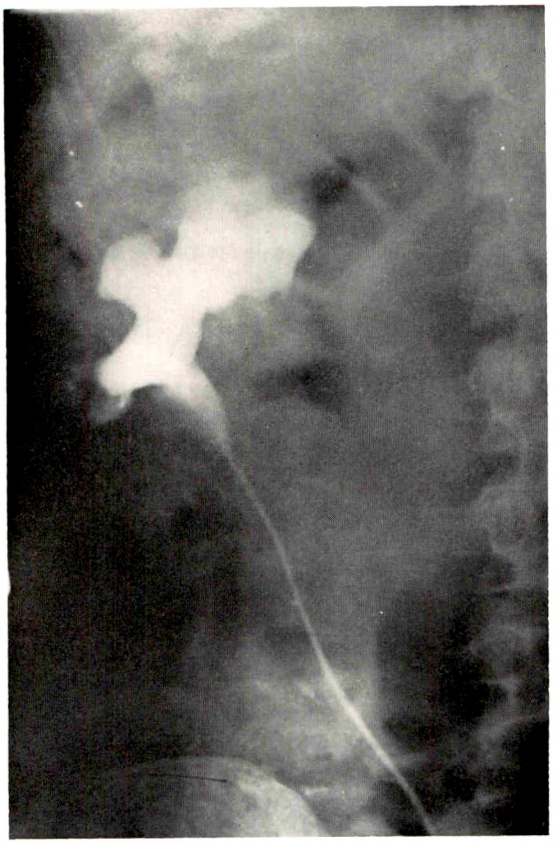


Fig. 2. Retrograde pyelogram in a case of lymphosarcoma of the right kidney. The kidney is displaced laterally. A soft tissue mass is present over the psoas muscle. There is moderate dilatation of the collecting system. The renal pelvis and inferior calyces are compressed.

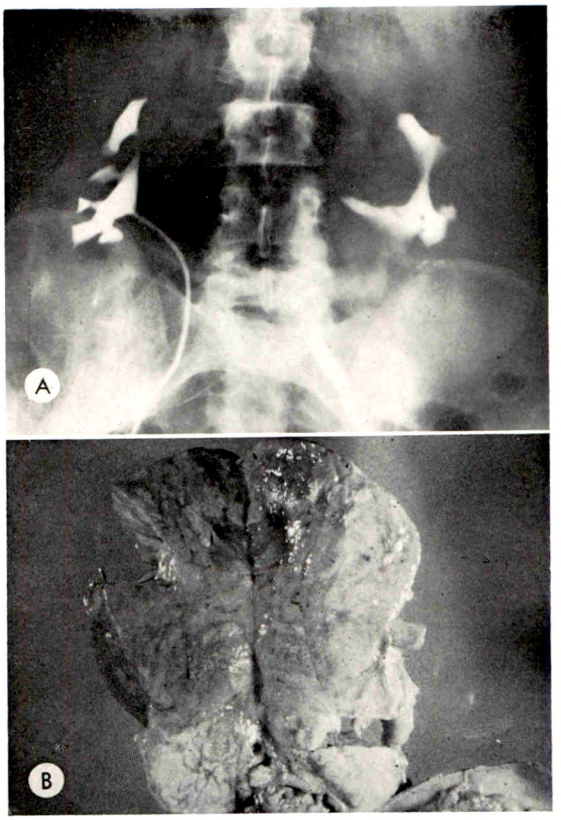


Fig. 3. (*A*) Excretory urogram in a case of lymphosarcoma of both kidneys. The lower half of the left kidney is considerably enlarged. There is marked deformity of the left collecting system with elongation, compression and blunting as well as an increased cortical thickness. The right kidney shows some blunting of the calyces and narrowing of the infundibulum to the superior calyx. (*B*) Autopsy specimen of the right kidney. The renal parenchyma is diffusely infiltrated by the neoplasm.

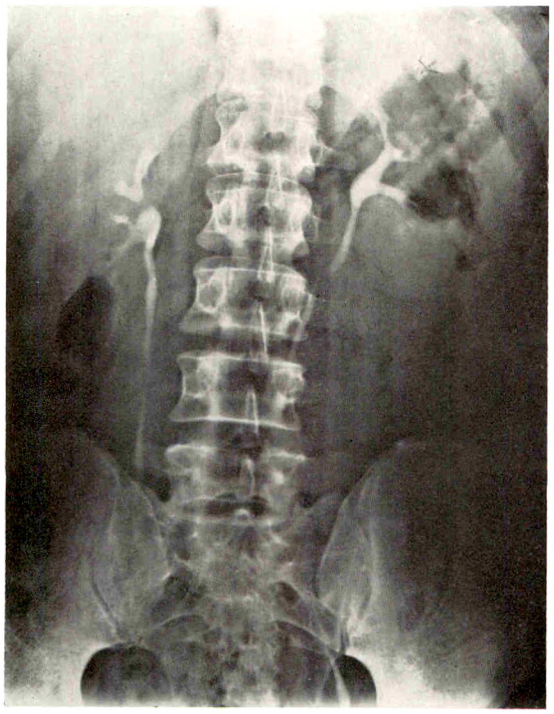


FIG. 4. Lymphosarcoma of both kidneys. The inferior pole of the left kidney is enlarged. The right collecting system is normal. On the left the inferior calyx is compressed and the renal cortex surrounding this calyx is of increased thickness. The proximal left ureter is deviated medially.

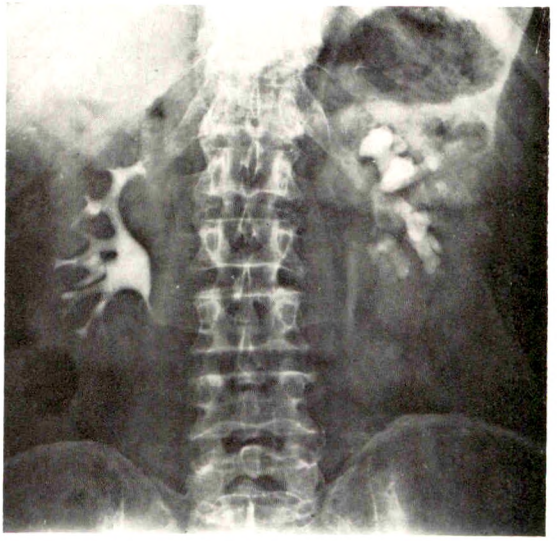
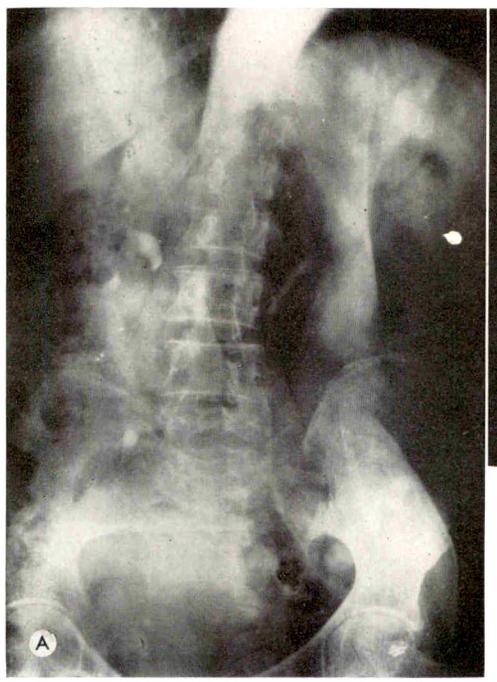


FIG. 5. Lymphosarcoma of the left kidney. There is an irregular enlargement of the lower pole of the left kidney. The left collecting system is moderately dilated and multiple defects are present in the pelvis and proximal ureter. The inferior calyx is compressed with an increased cortical thickness. The right kidney is normal.



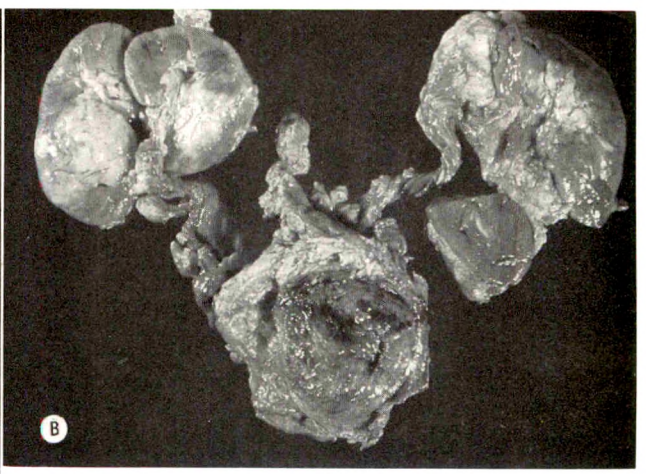


FIG. 6. (*A*) Intravenous urogram in a case of Hodgkin's disease of both kidneys. The cortex of the right kidney is increased in thickness. The calyces are compressed. There is poor visualization of the left collecting system. (*B*) Autopsy specimen shows tumor in both kidneys with a localized mass of neoplastic tissue in the lower portion of the right kidney.

kemia. Two of the 3 patients with reticulum cell sarcoma also had enlargement of the liver and spleen. Almost one-half of the patients demonstrated a mass in the renal area, while pain and tenderness in this region were encountered in about one-third of the patients.

Hematuria was a significant finding and was noted in about one-half of the patients. In the majority of instances this was microscopic. The less specific signs of albuminuria and pyuria occurred in about one-half of the cases.

In two-thirds of the patients there was an interval of less than one year from the time of the microscopic diagnosis of the neoplastic process to the roentgen detection of the renal involvement. The roentgen and clinical evidence of renal involvement by lymphoma or leukemia indicates an ominous prognosis. This was confirmed by the



FIG. 7. Hodgkin's disease of the left kidney. Obliteration of the left psoas muscle with lateral displacement of the left kidney. Splenomegaly. The right collecting system is normal. On the left there is elongation and thinning of the major calyces with an increase in the renal cortical thickness.

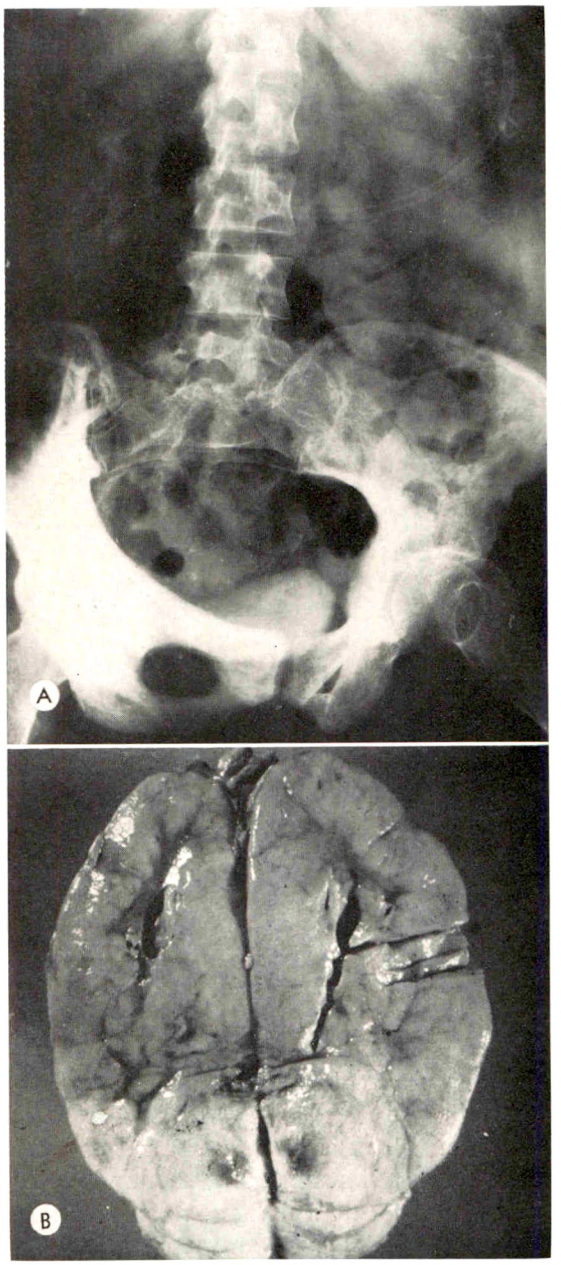


FIG. 8. (*A*) Intravenous urogram in a case of Hodgkin's disease of the left kidney. A decompression tube is in place within the stomach. The left kidney is markedly enlarged especially at the lower pole and the collecting system is not visualized. The excretion is poor on the right with some dilatation of the renal pelvis. (*B*) Surgical specimen of left kidney. The renal parenchyma is completely replaced by tumor with a localized mass at the inferior pole.



FIG. 9. Reticulum cell sarcoma of both kidneys. The kidneys are enlarged. There is marked narrowing and elongation of the left collecting system simulating the appearance of a polycystic kidney. On the right, similar changes are present with dilatation of the pelvis.

observation that about two-thirds of the patients died less than 4 months after the roentgen diagnosis of renal involvement was made.

The plain roentgenograms of the abdomen were helpful in the detection of renal abnormality in about two-thirds of the cases, showing localized or generalized renal enlargement. The roentgen modality and physical examination were about equal in the accuracy of splenic and liver enlargement.

Decrease in the renal function was seen in about one-third of the cases, being unilateral in 5 and bilateral in 6. Only one of the 4 patients with lymphatic leukemia showed decreased renal function, whereas the remainder of the patients had either lymphosarcoma or Hodgkin's disease.

The significant findings on intravenous urography were an increase in the renal

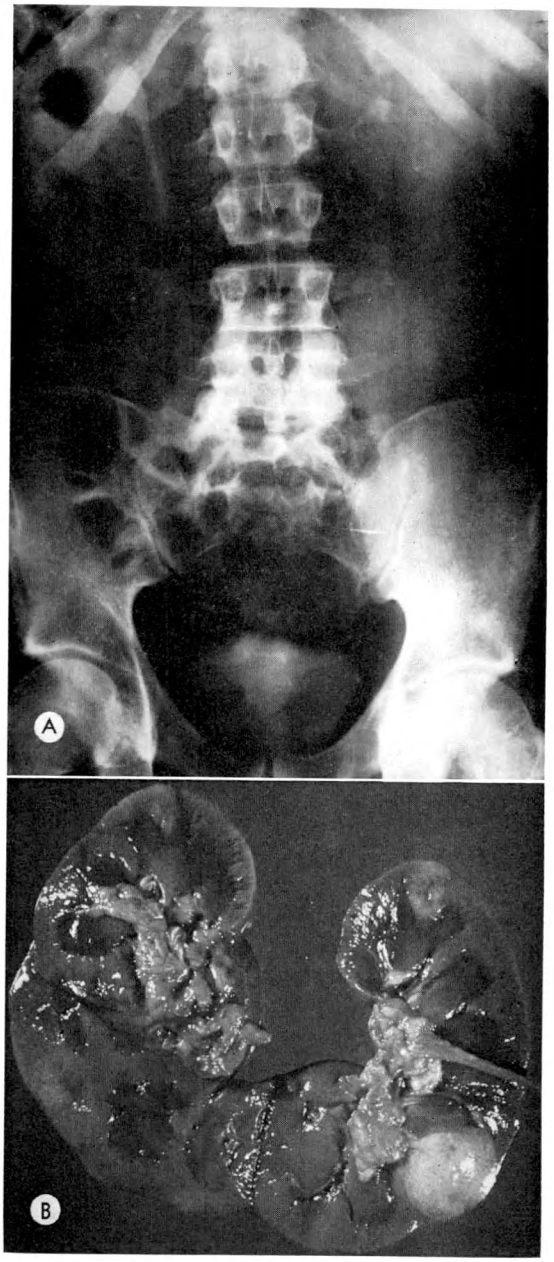


FIG. 10. (*A*) Intravenous urogram in a case of reticulum cell sarcoma of both kidneys. There is compression of the left renal pelvis and calyces with an increased cortical thickness. The minor calyces of the right kidney are also compressed. (*B*) Autopsy specimen shows tumor infiltrates and nodules in both kidneys. A 3 cm. nodule is noted in the lower portion of the left kidney.

cortical thickness and deformity of the collecting system. Both abnormalities were present in 3 of the 4 patients with lymphatic leukemia. A deformed collecting

system was the more frequent finding with malignant lymphoma, all of the reticulum cell sarcoma patients showing this abnormality.

The most common pattern of deformity of the collecting system indicated a diffuse infiltration. This was encountered in all of the patients with reticulum cell sarcoma and lymphatic leukemia. Single or multiple nodules were seen only in the malignant lymphomas, and multiple nodules occurred only with lymphosarcoma.

From the correlation of the urogram with the postmortem examination, it was evident that lymphatic leukemia and reticulum cell sarcoma involved both kidneys. Only 4 cases (2 lymphosarcoma and 2 Hodgkin's disease) were encountered with unilateral renal neoplasm at autopsy.

TREATMENT

Since involvement of the parenchyma of the kidneys by lymphoma is, with very rare exceptions, a manifestation of a generalized disease in an advanced form, currently available therapy is generally not effective. However, we feel that local irradiation of the involved kidney constitutes the most effective treatment in such a situation. The use of alkylating agents, as well as antimetabolites, is bound to increase the load upon the kidneys and influence the azotemia adversely. External irradiation is capable of improving diuresis and reducing the extent of kidney involvement more efficiently than most of the systemic agents currently in use.

We have recently seen a 29 year old female with lymphosarcoma involving the kidney (not included in the present series of 20 cases) in which a subjective as well as objective response was obtained for 6 months after radiation therapy to the kidney region. The patient ultimately succumbed to her disease 6 months after the manifestation of the kidney involvement.

Several other attempts at local irradiation of the kidneys in similar types of patients manifesting oliguria or anuria resulted in only meager response. However, therapy in all instances was given very late and actually only in the terminal stage of the disease, in some cases, because of lack of early recognition of the kidney involvement.

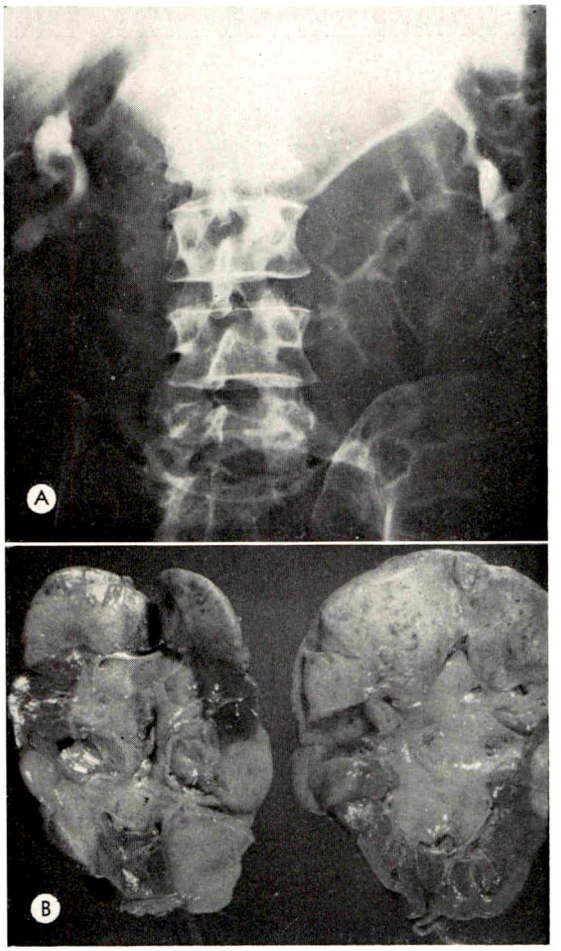


Fig. 11. (*A*) Reticulum cell sarcoma of both kidneys. A spheroid mass is present in the central portion of the right kidney with compression of the adjacent calyces and the pelvis. The left kidney is displaced laterally. The left middle and inferior calyces are blunted. (*B*) Autopsy specimen.

It is important in the management of the patient with malignant lymphoma to obtain a base line excretory urogram, and to follow the patient with periodic scout roentgenograms or intravenous urograms for the obvious signs of kidney involvement. Renal abnormalities on pyelography will usually precede the rise of the blood urea nitrogen. Although the ultimate course is not influenced, temporary remission of azotemic signs and symptoms may be ac-

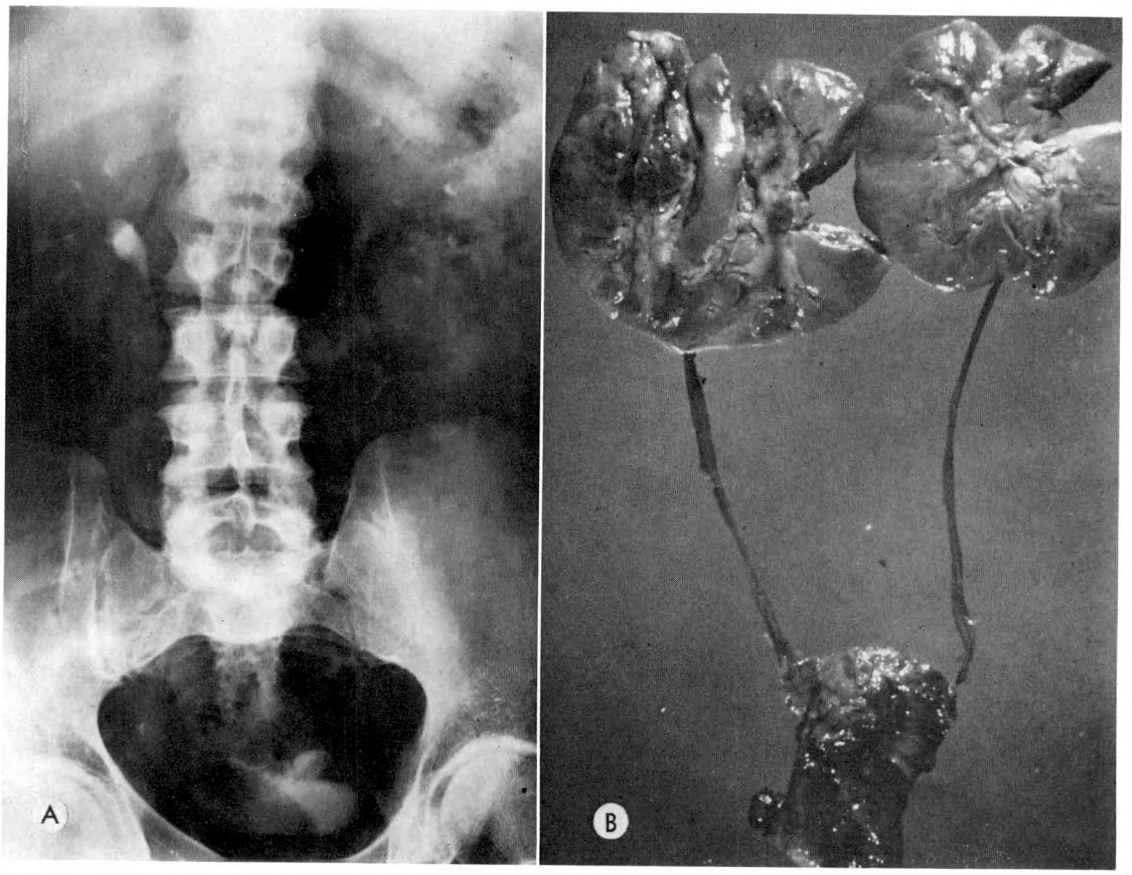


FIG. 12. (*A*) Lymphatic leukemia of both kidneys. The infundibula are narrowed throughout each kidney. The minor calyces are compressed. The right renal cortex is thickened. (*B*) Autopsy specimen shows diffuse tumor infiltrates in both kidneys.

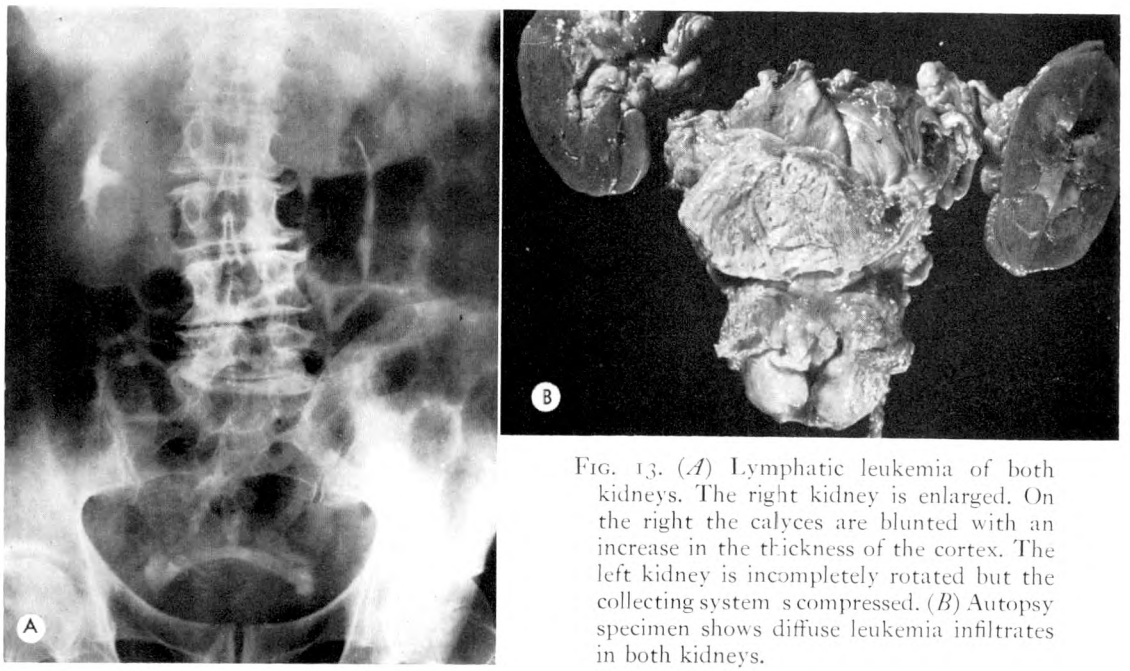


FIG. 13. (*A*) Lymphatic leukemia of both kidneys. The right kidney is enlarged. On the right the calyces are blunted with an increase in the thickness of the cortex. The left kidney is incompletely rotated but the collecting system is compressed. (*B*) Autopsy specimen shows diffuse leukemia infiltrates in both kidneys.

complished, and at least several months of reasonably comfortable survival may be procured.

SUMMARY AND CONCLUSION

1. A series of 20 cases of lymphoma and leukemia in adults (histologically verified) are presented.

2. Tabular summaries of the age incidence, types of lymphoma microscopically, the findings on physical examination, the significant laboratory data, the evaluation of the plain roentgenograms of the abdomen and the excretory urograms, and the correlation of urographic and postmortem findings are given.

3. A review of the literature as it relates to the pathologic aspects and the roentgen findings of renal lymphoma and leukemia is made.

4. It is stressed that although lymphoma or leukemia may first become manifest in the kidney, much of the kidney involvement is generally encountered late in the course of these neoplastic diseases. A rising blood urea nitrogen in the presence of hematuria, albuminuria, or pyuria, together with enlargement of the kidney, poor opacification on excretory urography, a deformed collecting system and thickening of the renal cortex, all should suggest the diagnosis of renal lymphoma or leukemia particularly in a patient in whom such a disease has been previously diagnosed in other structures.

5. The problem of therapy is discussed, and although radiation therapy to the kidney area is not curative, some palliation has been obtained. A trial of radiation therapy is thus considered worthwhile.

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NECROTIZING ENTEROPATHY: ROENTGENOGRAPHIC FEATURES*

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A REVIEW of autopsy material on 408 patients with leukemia or lymphoma treated at the City of Hope Medical Center from July, 1956 to July, 1961 revealed that necrotizing enteric lesions were present in 69 instances.[1] Three additional cases have been seen since the first report was made. Roentgenograms of these patients were studied to determine whether there were any clues to indicate the development of necrotizing enteropathy.

MATERIAL AND METHODS

The primary diagnoses of the patients with necrotizing enteropathy were leukemia in 65 cases and lymphoma in 7. There were 41 male and 31 female patients and the ages ranged from 15 months to 67 years with an average age of 32 years. These patients had received a variety of medications in their terminal weeks of life. Antibiotics had been administered almost routinely.

The roentgenograms of this group of patients were considered to have possible significance if they were made within 2 weeks prior to death. Recent roentgenograms of the chest, abdomen or both regions were available for study in 56 cases.

PATHOLOGY

A common factor in the 72 cases in our series was necrosis of mucosal surfaces creating a portal of entry for enteric organisms. The cases could be divided into 4 groups based on pathogenesis.

GROUP 1—SHOCK

Shock with ischemia or vascular stasis was probably responsible for the more superficial variety of intestinal mucosal necrosis. The ulcerations with a covering pseudomembrane were occasionally discrete, but commonly formed large confluent patches or involved long segments of the gastrointestinal tract. Clinical shock was described in almost every patient in this group. Necrotic leukemic infiltrates were not present. Examples of so-called "pseudomembranous enterocolitis" fell into this group.

GROUP 2—NECROSIS OF GASTROINTESTINAL INFILTRATION FROM CHEMOTHERAPY

Necrosis of tumor or leukemic infiltrates and mucosal ulcerations permitted enteric organisms to enter the mucosa and submucosa. The necrotizing character of many of these organisms and diminished host resistance (as a consequence of the leukemia or lymphoma and/or corticoid therapy) apparently led to rapid extension of the necrosis to include large segments of intestinal tissue. The lesions were most frequent in the terminal ileum, appendix, cecum, and ascending colon. Complications included acutely inflamed, gangrenous or ruptured appendices, and necrosis with perforation of the small and large intestines. The majority of Group 2 patients were leukopenic or in an acute blastic crisis. Cases of so-called "ileocecal syndrome"[2] would fall in this category.

GROUP 3—HEMORRHAGIC DIATHESIS AND MUCOSAL NECROSIS OVER HEMORRHAGES DUE TO THROMBOCYTOPENIA

Mucosal ulcerations overlying hemorrhages occurred in any portion of the gastrointestinal tract, although most commonly in the colon.

GROUP 4—STASIS AND STERCORAL OR DECUBITAL MUCOSAL EROSIONS

These were most common in the esophagus and rectosigmoid. Trauma from

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passage of food, gastric tubes, or vomiting may have initiated the esophageal ulcers. Inspissated feces, enema tubes, or thermometers may have traumatized the rectosigmoid mucosa and afforded entrance to enteric organisms or fungi. The sequence of events following bacterial invasion is similar to that of Groups 1, 2, and 3, consisting of further necrosis, mucosal ulcerations, gross bacterial and/or fungal infestations, and, in some, rectosigmoid perforations.

Combinations of Groups 1, 2, 3, and 4 were common. Bacteremia with enteric bacteria and bacterial shock was a frequent event.

ILLUSTRATIVE CASES

GROUP 1 ENTEROPATHY

CASE 1. A 15 month old female infant (C.O.H. No. 61-1030) was referred with a diagnosis of acute lymphocytic leukemia established by the examination of bone marrow and peripheral blood at another institution. She had a 2 week history of swelling in the scalp and petechiae on the back and chest. There were hepatosplenomegaly and elevated temperature. The admission hematologic examination showed: hematocrit 47 per cent, white blood cell count 3,050 per cu. mm. with 99 lymphocytes and 1 per cent prolymphocytes, platelets 30,000 per cu. mm. She was started on penicillin and 50 mg. per day of prednisone.

The patient's temperature spiked to 104°F. on the third and fourth hospital days. The next day her abdomen was tense and tender. The temperature remained elevated and the white blood cell count fell to 1,350 per cu. mm. *Pseudomonas aeruginosa* was cultured from the blood. Chloromycetin and terramycin were added to her intravenous medications.

On December 10 abdominal distention again was striking after a temporary improvement. On December 11 surgical consultation and roentgenographic evaluation (Fig. 1, *A* and *B*) led to a diagnosis of a perforated viscus. However, the patient was moribund and surgery was not advised. The patient died the next day, 17 days after admission and a little over a month after leukemia had been diagnosed.

At postmortem examination there were no leukemic infiltrates in the bone marrow or viscera. Death was attributed to peritonitis which developed after multiple perforations appeared in necrotic areas in the small intestine (Fig. 1*C*).

GROUP 2 ENTEROPATHY

CASE 11. An 8 year old boy (C.O.H. No. 57-384) was admitted on April 1, 1957 with intermittent pains in the extremities and low grade fever of 2 months' duration. Pallor, anorexia and listlessness had been present for 1 month.

The diagnosis on admission was acute lymphoblastic leukemia. Hematocrit was 22 per cent, white blood cell count 4,040 per cu. mm. with polymorphonuclear leukocytes 2 per cent, lymphocytes 58 per cent, immature abnormal cells 40 per cent, and platelets 64,000 per cu. mm. The bone marrow showed sheets of lymphocytes and immature cells resembling lymphoblasts. He was started on TAF (thiol activating factor). There was no improvement and on April 17 he was started on prednisolone. Transfusions were given as needed. He responded relatively well, showing a decrease in the size of the spleen and lymph nodes and also a drop in the white blood cell count.

The patient was re-admitted on February 16, 1958, because of cough and daily temperature spikes up to 104°F. On February 20 he was febrile, with right lower quadrant tenderness. He was started on chloromycetin. On February 23 he had generalized tenderness (more marked in the right lower quadrant) with considerable guarding. The clinical and roentgenographic impression (Fig. 2*A*) on February 25 was that he had a right lower quadrant abscess on the basis of a perforated appendix. Exploration was recommended. An appendectomy was done on the following day. The appendix was gangrenous, and the anterior wall of the cecum was indurated. *Pseudomonas aeruginosa* was cultured from the abdomen at the time of surgery. Postoperatively, he received fresh blood. On the morning of February 27, the child was jaundiced and appeared to be in shock. Hematocrit was 40 per cent, despite marked pallor. He became increasingly dyspneic throughout the day and expired that afternoon.

Autopsy showed submucosal hemorrhages in the esophagus and stomach and petechiae throughout the small bowel which was diffusely dilated. The ileocecal valve was edematous and hemorrhagic. The mucosa and muscularis of the first 10 cm. of colon above the valve were

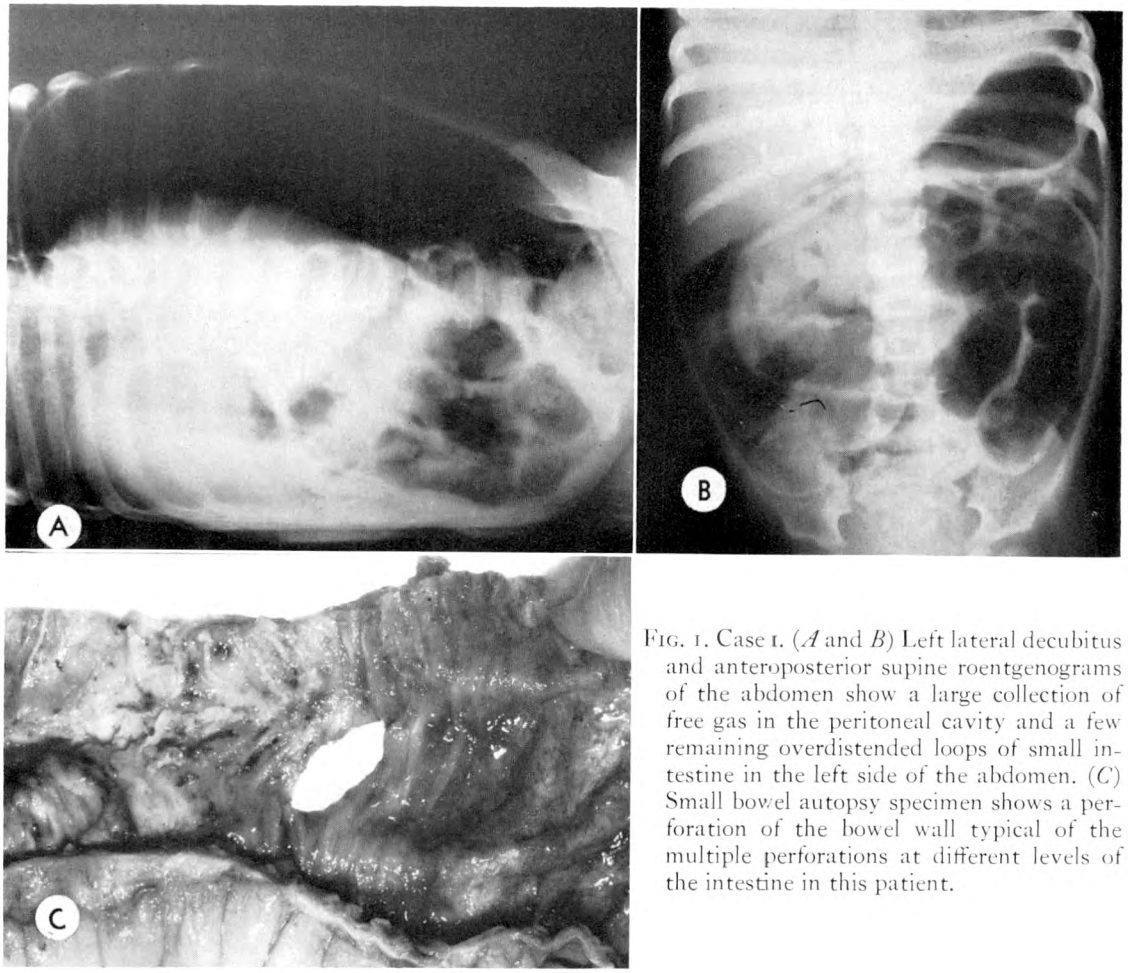


FIG. 1. Case I. (*A* and *B*) Left lateral decubitus and anteroposterior supine roentgenograms of the abdomen show a large collection of free gas in the peritoneal cavity and a few remaining overdistended loops of small intestine in the left side of the abdomen. (*C*) Small bowel autopsy specimen shows a perforation of the bowel wall typical of the multiple perforations at different levels of the intestine in this patient.

absent. Many ulcerations were present throughout the colon from the distal third of the ascending colon to the mid-descending colon (Fig. 2*B*). These ulcers occurred in areas of leukemic infiltration. Similar infiltrates could be identified in the appendectomy specimen. Fungi were superimposed on the ulcers. The patient also had an acute myocarditis, probably secondary to a pseudomonas bacteremia.

CASE III. A 9 year old boy (C.O.H. No. 59–77) was admitted on January 21, 1959 with a referral diagnosis of malignant cervical lymphadenopathy. One year prior to admission he developed a swelling in the left side of the neck. This was treated as infectious lymphadenopathy secondary to an ear infection. However, the lymphadenopathy persisted and a biopsy on January 9, 1959, showed a malignant lymphoma, lymphoblastoma type.

On admission, he had a hematocrit of 25 per cent and appeared pale. Corticoids (medrol, 50 mg. daily) were started on January 23. On February 3 the dose was progressively decreased to a maintenance level of 5 mg. twice daily. The left neck was treated with cobalt 60 irradiation to a dose of 2,804 rads. The neck masses showed good regression. The patient was subjectively better for a few days but he developed abdominal pain and frequent vomiting. Gastrointestinal survey (Fig. 3, *A* and *B*) showed multiple polypoid lesions throughout the gastrointestinal tract. Cobalt 60 irradiation to the entire abdomen was begun on March 3, but discontinued on March 9 due to the moribund condition of the patient. He expired on March 10, 1959.

Necropsy showed extensive lymphomatous involvement of almost all organs. There was extensive infiltration throughout the gastro-

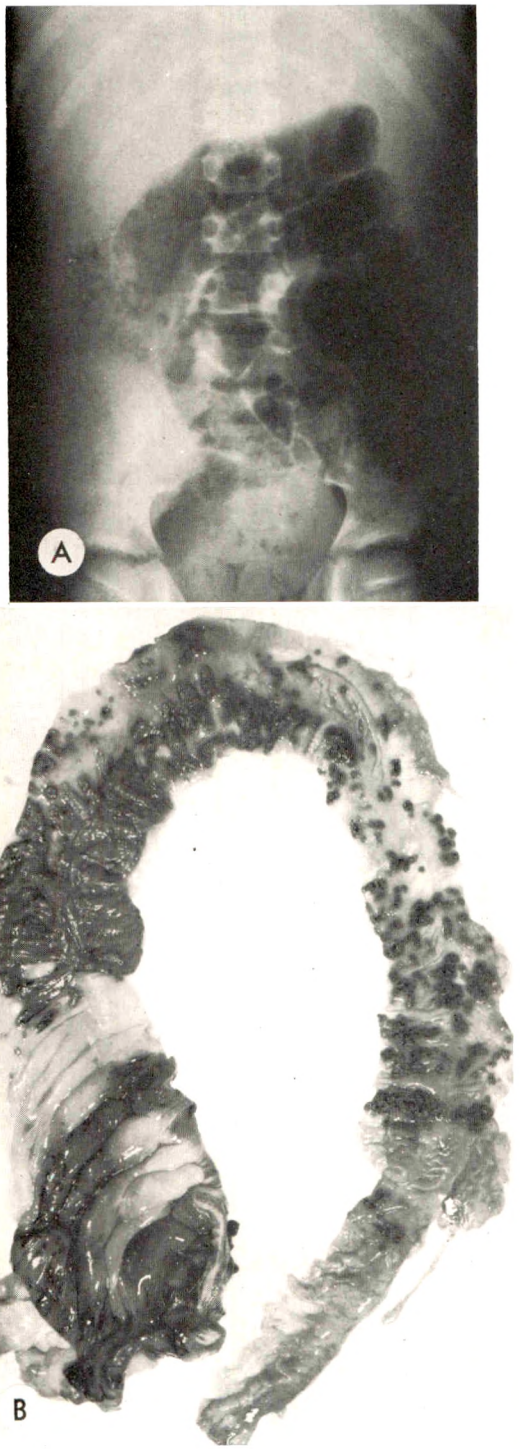


Fig. 2. Case II. (*A*) Anteroposterior roentgenogram of the abdomen shows soft tissue density in the right lower abdomen displacing overdistended loops of small bowel. (*B*) Autopsy specimen of colon shows edematous and hemorrhagic ileocecal valve with zone adjacent to the valve denuded of mucosa. Note many ulcers, some confluent, starting at the level of the distal third of the ascending colon and extending to the mid-descending colon.

intestinal tract with the formation of numerous superficially ulcerated tumor nodules, so-called "pseudoleukemia gastrointestinalis" (Fig. 3*C*). The ulcerated zones were probably the portals of entry for hemolytic *Staphylococcus aureus* and *alkaligenes fecalis* organisms which were cultured from blood at autopsy.

Case IV. The patient, a 15 year old white girl (C.O.H. No. 60–526), was admitted in June, 1960 complaining of fatigue and "spots" on her legs. On examination, she was found to have petechiae and ecchymoses. Her total white blood cell count was 11,000 per cu. mm. (50 per cent lymphocytes, 34 per cent prolymphocytes and 15 per cent blast forms). The hematocrit was 24 per cent. The platelet count was 20,000 per cu. mm. She was treated with adrenal cortical hormones resulting in striking clinical improvement including disappearance of ecchymoses and splenomegaly. On July 29, marrow examination revealed a somewhat hypoplastic marrow with an essentially normal cell population. She had been discharged for only 2 days when she was re-admitted because of severe abdominal pain. Roentgenograms of the chest and abdomen showed free air in the peritoneal cavity and an abscess in the right lower quadrant displacing the bowel gas pattern (Fig. 4, *A*, *B* and *C*). She underwent abdominal exploration on the same day (July 31, 1960). A perforation of the colon was found with generalized peritonitis. Hemicolectomy was performed. The surgical specimen showed two perforations in the right colon near the cecum and on microscopic study inflammatory reaction as well as leukemic infiltration of the mucosa (Fig. 4*D*).

The patient did well for a time but subsequently developed an ileal fistula. Late in September, when she was in hematologic remission, she was again explored and the fistula was closed. This procedure was well tolerated and she was discharged on October 11, 1960. She was re-admitted on December 19 in shock with a temperature of 105° F. and nausea and vomiting. She was treated with antibiotics, corticosteroids and adrenergic drugs. Despite these measures, her blood pressure continued to fall and she expired the following day, nearly 5 months after her hemicolectomy.

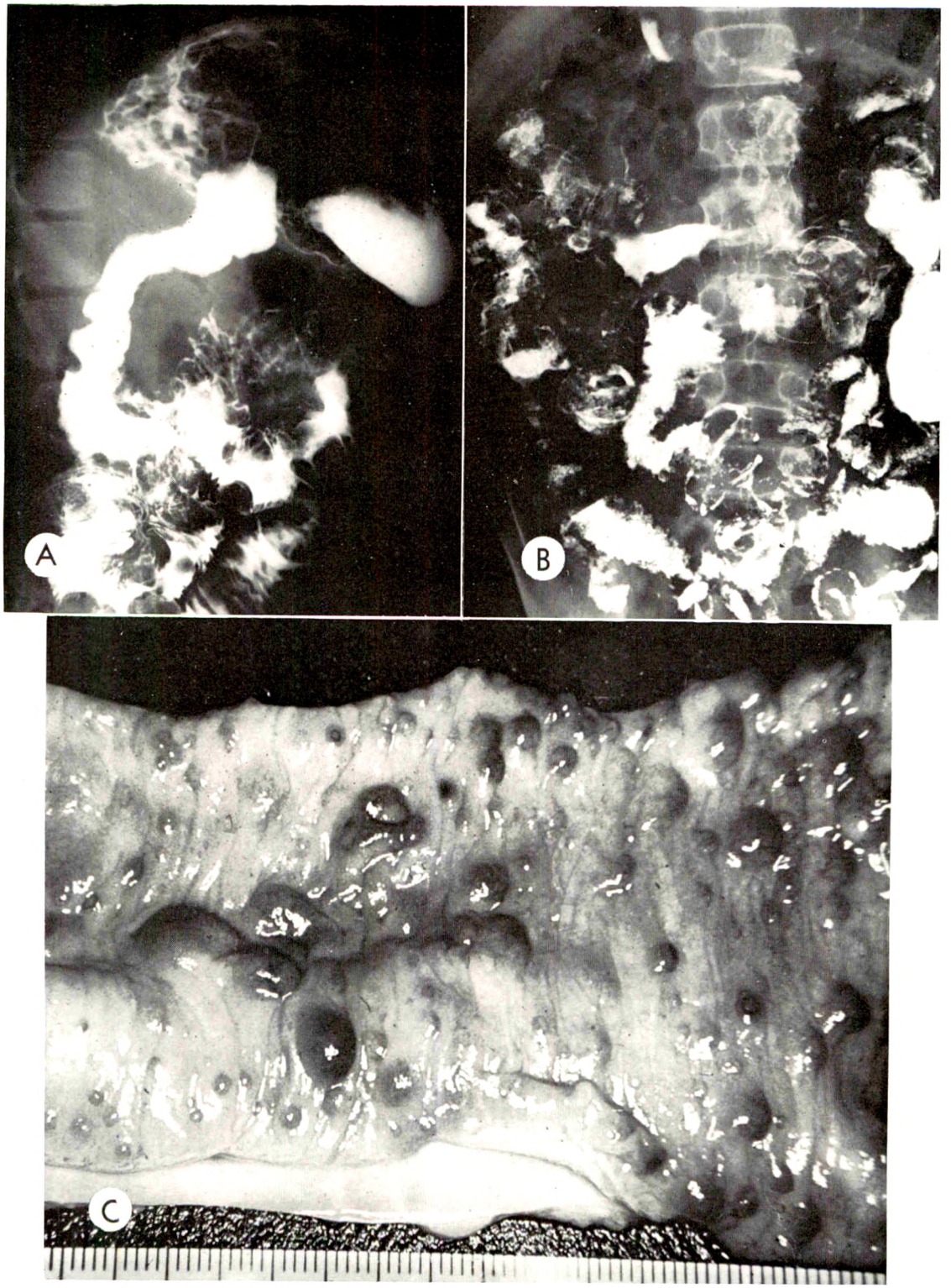


FIG. 3. Case III. (*A*) Lateral roentgenogram early in gastrointestinal study shows large polypoid filling defects in the stomach, duodenum and jejunum. (*B*) Posteroanterior roentgenogram 3 hours after the barium meal shows polypoid filling defects throughout the small intestine with some dilated segments due to partial obstruction. (*C*) Gross specimen of a segment of small intestine shows some of the nodular masses responsible for the filling defects seen on the barium studies.

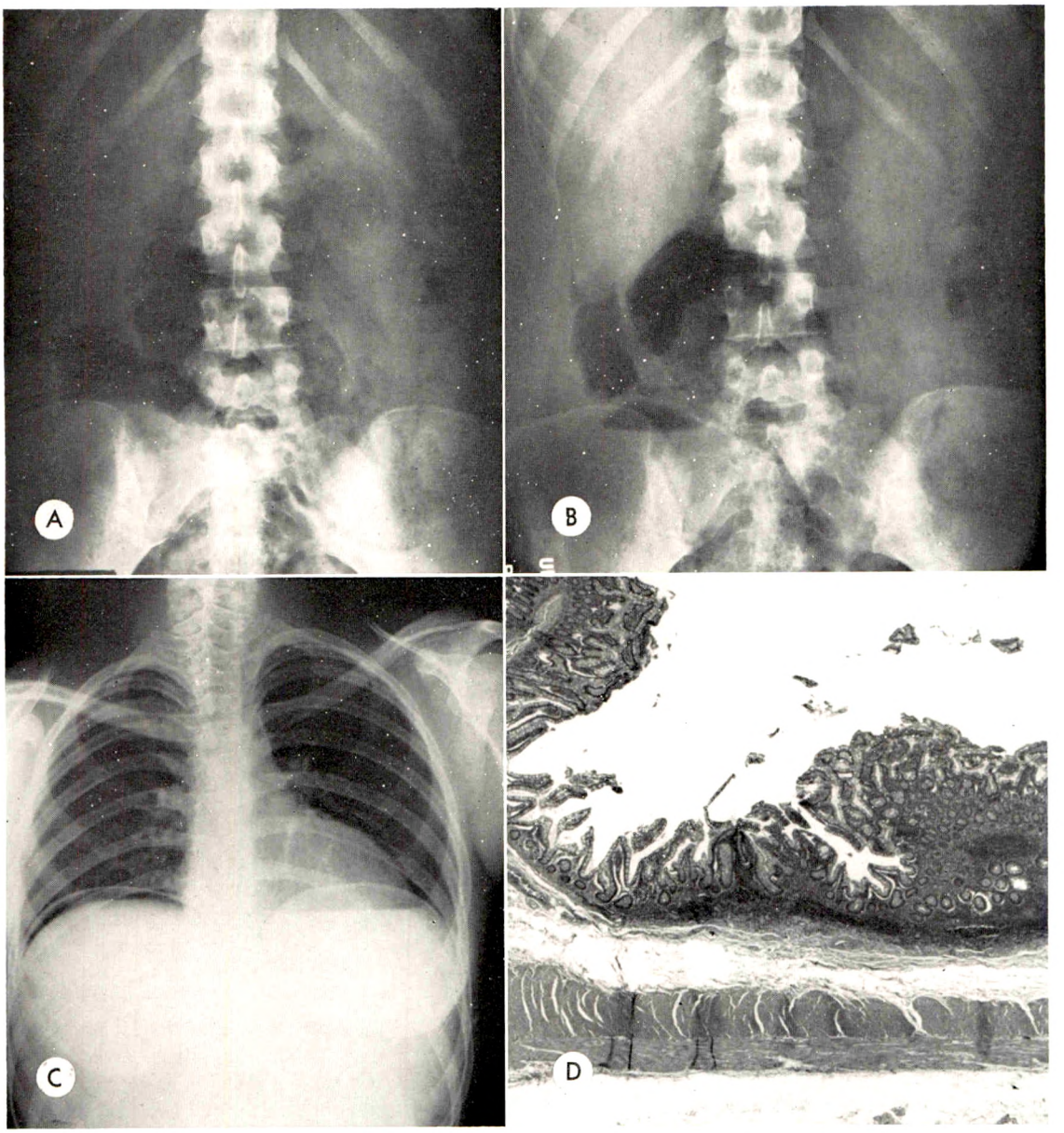


Fig. 4. Case iv. (*A*) Supine roentgenogram of the abdomen shows right lower quadrant mass with soap bubble pattern of radiolucencies indenting the gas shadow of adjacent segment of bowel. (*B*) Upright roentgenogram of the abdomen shows air-fluid level within the abscess which indented the bowel gas pattern on the supine roentgenogram. (*C*) Posteroanterior chest roentgenogram shows free air under the right hemidiaphragm. (*D*) Section from surgical specimen of colon adjacent to the perforation site reveals inflammatory reaction and leukemic infiltration of the mucosa (magnification ×50).

At autopsy the anastomosis of the bowel as well as the remainder of the gastrointestinal tract appeared unremarkable. The liver and bone marrow were extensively involved by the leukemic process.

Group 3 Enteropathy

Case v. A 5 year old girl (C.O.H. No. 55–386) was admitted on March 17, 1955. She had been evaluated at another institution in January, 1955 because of poor appetite and marked

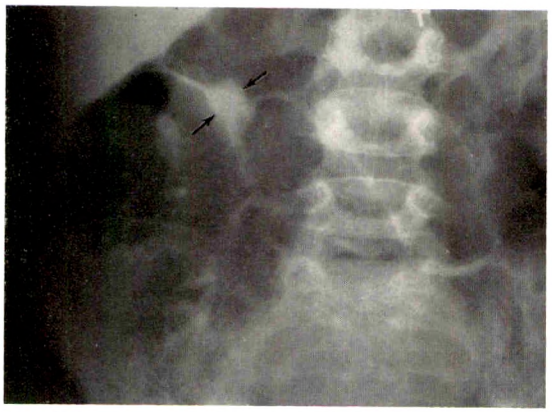


FIG. 5. Case v. Detail of right lower abdomen from an anteroposterior roentgenogram of the abdomen shows overdistended small bowel loops. A mass indenting ileum was found near ileocecal valve at site of a hemorrhagic mass found at autopsy. The bowel gas pattern was persistent on several roentgenograms.

pallor. A diagnosis of acute lymphatic leukemia was made. Therapy with 6 MP (purinethal) was started but there was no improvement. She was transferred to the City of Hope Medical Center for further management. She presented with multiple bruises over her extremities and buttocks. The abdominal organs were not palpable. Leukopenia, neutropenia and thrombocytopenia with a differential consisting predominantly of lymphocytes were present. Bone marrow aspiration biopsy was compatible with lymphatic leukemia. Her hemoglobin dropped from the admission level of 10.5 gm. per cent to 4.4 gm. per cent. She received multiple transfusions of packed red blood cells and an additional course of 6 MP. On her last admission, September 15, 1955, hepatosplenomegaly, diffuse lymphadenopathy and hemoglobin levels as low as 2.4 gm. per cent were noted. A roentgenogram of the abdomen made on October 21, 1955 (Fig. 5) showed distended loops of small intestine and a questionable nodular indentation of the terminal ileum. She became progressively weaker and developed abdominal distress with nausea, vomiting, and passage of blood streaked mucus per rectum on October 27. She expired the next day.

At autopsy multiple submucosal hemorrhages were found in the stomach and a small hemorrhagic nodule was present in the terminal ileum at the level noted on the abdomen roentgenogram.

GROUP 4 ENTEROPATHY

CASE VI. The patient was a 7 year old girl (C.O.H. No. 60–1063) who was known to have noncyanotic congenital heart disease. Subacute bacterial endocarditis had been treated elsewhere. She developed acute lymphocytic leukemia for which she was first admitted to the City of Hope Medical Center in December, 1960. She responded well to dexamethasone and methotrexate and was discharged in January, 1961, only to be re-admitted in February, 1961 with recurrence of endocarditis. She was treated with antibiotics and responded well. She was discharged in good hematologic remission. She was kept on maintenance doses of methotrexate.

She was re-admitted in November, 1961 with fever and petechiae and abdominal pain. Her leukemia was in relapse and 6 MP therapy was reinstituted. She was discharged slightly improved. The relapse of her leukemia persisted and steroid therapy was started.

The patient was re-admitted in December, 1961 because of anemia. She had increasingly severe rectal pain. Roentgenograms showed fecal retention (Fig. 6*A*). A barium enema examination revealed polypoid mucosal swelling of the rectal mucosa (Fig. 6, *B* and *C*). An ischiorectal abscess was diagnosed on December 12, 1961, and, after 4 days, there was some prolapse of rectal mucosa followed by sloughing of necrotic tissue. Her total white blood cell count was 1,400 per cu. mm. with 82 per cent segmented granulocytes; it subsequently rose to 13,000 per cu. mm. Although the platelets were adequate, petechiae appeared and recurrence of endocarditis was diagnosed. *Pseudomonas* was found on blood culture. The spinal fluid was cloudy and xanthochromic, with 7,200 red blood cells and 1,400 white blood cells per cu. mm., chiefly polymorphonuclear cells. On January 15, 1962, the patient had a grand mal seizure with flaccidity of her right arm and right side of her face. She went into shock and expired early the next morning.

At autopsy there were a septum primum defect and a widely patent foramen ovale. There were signs of healed endocarditis of the pulmonary valve and fresh vegetations were present on the mitral valve projecting into the left atrium. There were multiple hemorrhagic foci in the brain. The bone marrow and peripheral blood study showed a state of good remission of the child's leukemia.

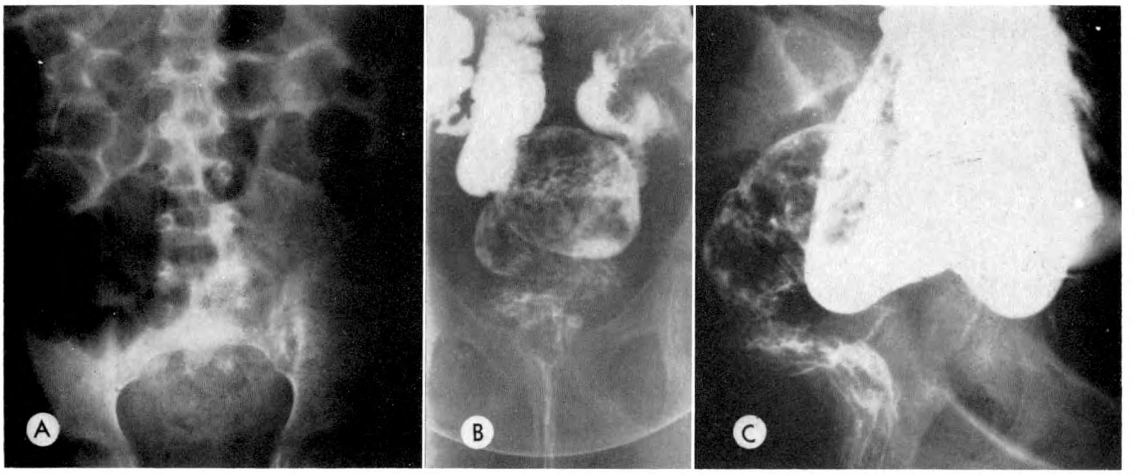


Fig. 6. Case vi. (*A*) Anteroposterior roentgenogram of the abdomen shows large collection of feces in the rectosigmoid and marked gaseous overdistention of the remainder of the intestine. (*B* and *C*) Postero-anterior and lateral barium enema studies show polypoid mucosal pattern in the rectum, persistent on pre- and postevacuation roentgenograms.

Case vii. A 69 year old female (C.O.H. No. 57–723) was admitted on June 26, 1957 with a history of anemia and congestive heart failure. Subacute granulocytic leukemia was diagnosed by bone marrow aspiration. She was treated with steroids and transfusions with initial improvement. In August, bone marrow study showed increasing activity of leukemia. She went into congestive heart failure. Chest roentgenograms (Fig. 7) revealed massive consolidation and fluid in the right chest. The patient went into shock and expired on August 15, 1957.

At autopsy there was diffuse ulceration and submucosal hemorrhage of the lower two-thirds of the esophagus. Old and recent ulcers with overlying clotted blood were present in the gastric antrum. Microscopic examination showed a membrane of necrotic material and blood over the desquamated areas of the esophagus and stomach. These zones were infiltrated with leukocytes, leukemic cells, mycelia and encapsulated yeast.

The right lung was firm throughout and contained numerous abscesses.

Case viii. A 36 year old male (C.O.H. No. 57–422) was first seen in the out-patient department on April 11, 1957, with a history of fever, sweats, weight loss, itching, splenomegaly and anemia. Hodgkin's disease was diagnosed 2 years previously by cervical lymph node biopsy. Radiation therapy with 1,400 rads to the left neck resulted in regression of the neck lymph nodes. A few months prior to his out-patient visit here, he received 500 rads to the mediastinum because of "increased markings" in the lung fields. When seen by us, it was felt that he had generalized Hodgkin's disease and he was placed on chlorambucil treatment. He had initial subjective improvement, although his spleen increased in size and he required multiple blood transfusions. In April, 1958, it was felt that chlorambucil was no longer controlling his disease. He was hospitalized for treatment with U-8344 (uracil mustard) and prednisolone, but responded poorly. He developed jaundice, septicemia and bleeding from the nose and gastrointestinal tract requiring multiple blood transfusions. He became cachectic and developed rales over the entire chest. Roentgenograms showed pneumonitis in the lung bases and fluid in the left base. There was widening of the mediastinal reflection behind the left heart shadow (Fig. 8, *A*, *B* and *C*). The patient was placed on antibiotics; however, he went into a state of shock, became comatose and expired on June 13, 1958.

At postmortem examination, the lower esophagus showed many deep ulcerations the bases of which were covered with a necrotic membrane (Fig. 8*D*). The colon had numerous mucosal hemorrhages and, in the ascending colon and cecum, elevated granular 1 to 2 mm. mucosal protrusions.

Both lungs were edematous, the right more

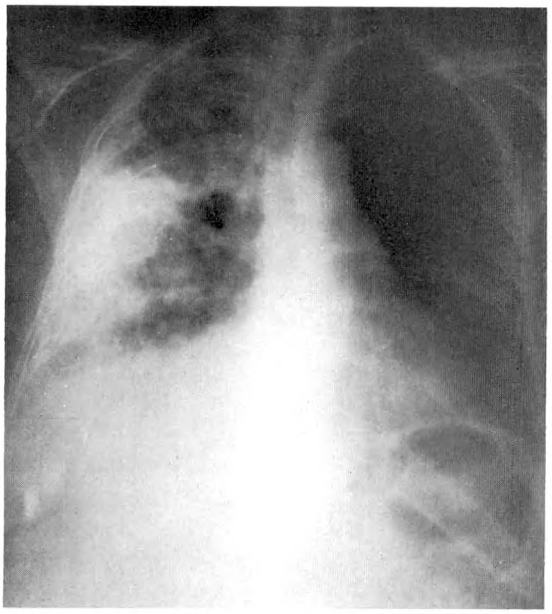


FIG. 7. Case VII. Posteroanterior chest roentgenogram shows massive consolidation interspersed with radiolucencies in the right hemithroax.

than the left. The right lung was hemorrhagic.

There was Hodgkin's sarcoma involvement of the esophagus at the areas of ulceration and in the colon. There was also involvement of many lymph nodes, liver, spleen and bone marrow.

ROENTGENOGRAPHIC FEATURES

Patients having Group 1 early mucosal ulcerations (5 cases, each combined with another grouping) showed a picture of paralytic ileus with generalized overdistention. Deeper ulcerations associated with pertitonitis presented a variable pattern of mechanical obstruction or of paralytic ileus (Fig. 1, *A*, *B* and *C*). The pattern may not be specific since combined pathologic types were present in each of the 5 patients.

The majority of the Group 2 lesions (12 cases, 3 of which were combined with other groups) presented with a pattern of obstructive ileus and a soft tissue density. The latter was related to inflammation associated with necrosis and often rupture of terminal ileum, appendix, cecum or ascending colon (Fig. 2, *A* and *B*; and Fig. 4, *A*, *B*, *C* and *D*). An extreme example of the pattern produced by nodular infiltration of the bowel is seen in the case of pseudoleukemia intestinalis (Fig. 3, *A*, *B* and *C*).

The Group 3 lesions (6 cases, 5 of which had combined type lesions) showed indirect evidence of bowel irritation with ileus and only rarely a direct sign of mass due to localized hemorrhage into the gastrointestinal tract (Fig. 5).

The Group 4 lesions (15 cases, 8 of which were combined with other type lesions) were mainly in the esophagus and colon. The rectosigmoid lesions behaved like low obstructing lesions showing little gas and feces in the rectosigmoid region and overdistention of the rest of the colon (Fig. 6, *A*, *B* and *C*).

It is interesting to note that esophageal lesions which fell into Group 2, 4 or both, showed a high associated incidence of pulmonary infiltrates possibly related to aspiration (Fig. 7). Only a few instances in which the ulcers were quite deep showed an increase in paramediastinal soft tissue shadows (Fig. 8, *A*, *B* and *C*). In 14 of 17 patients (82 per cent) with esophageal involvement, there were pulmonary infiltrates.

DISCUSSION

A more complete review of the pathology and clinical patterns of necrotizing enteropathy was presented in an earlier paper.[1] A brief survey of the problem may be helpful here. Several features of the disease entity may be related to the manner in which the primary disease, leukemia or lymphoma, was treated. Antibiotics are used more frequently and often in massive doses. Their use may permit overgrowth of normal intestinal flora by resistant bacteria or fungi which in turn may become invaders of necrotic areas.[13] The use of corticoids or various chemotherapeutic agents may be another factor in the iatrogenic induction of necrotizing enteropathy.[7] One-third of the lesions in our patients (24 of 72 cases) were probably in good measure directly attributable to intensive antibiotic and chemotherapy. However, the problem was noted in acute leukemia before the era of modern

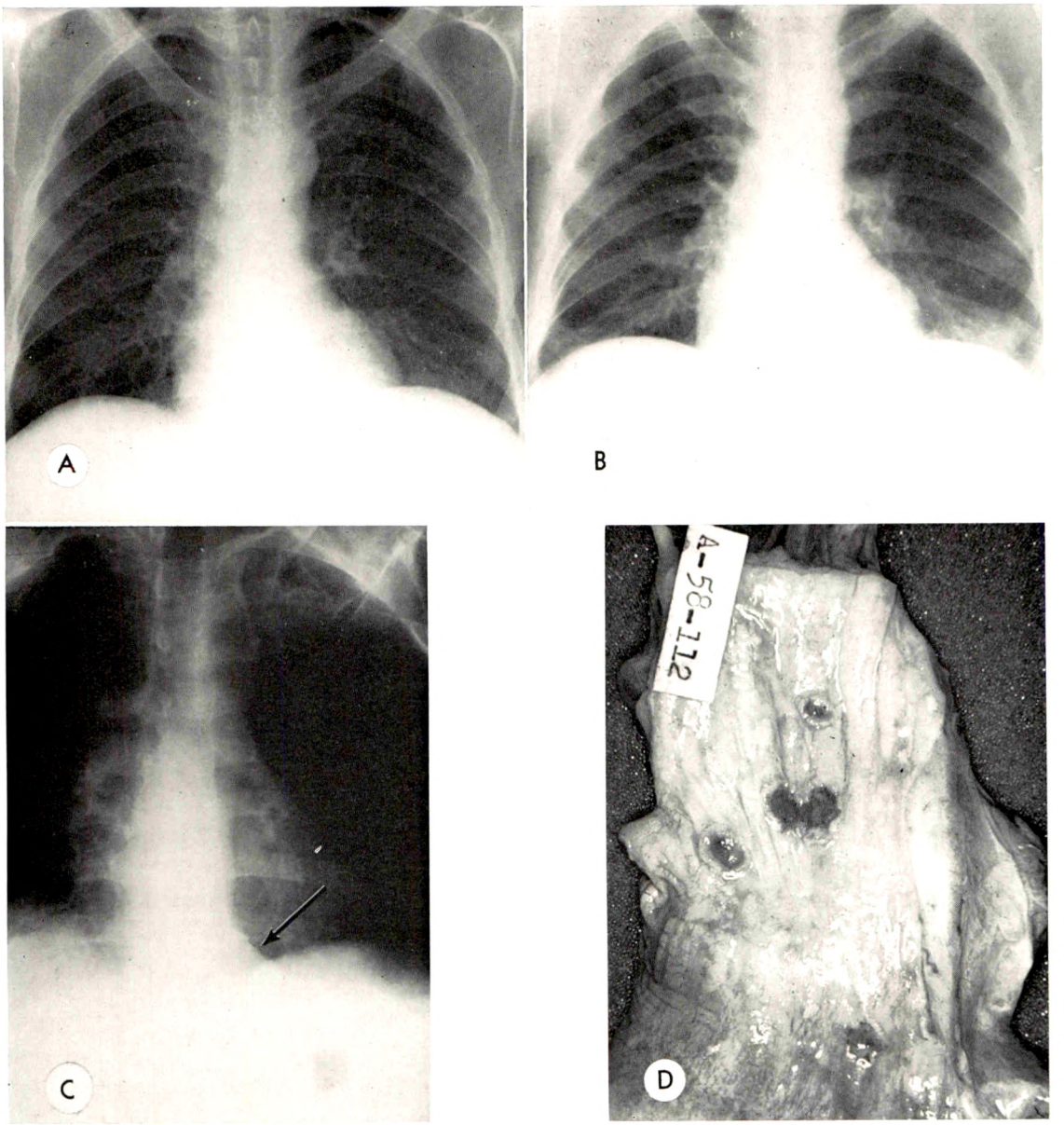


Fig. 8. Case VIII. (*A*) Posteroanterior chest roentgenogram on admission is normal except for slight elevation of the left hemidiaphragm due to splenomegaly. (*B*) Chest roentgenogram 10 days ante mortem shows linear infiltration in the left lung base. (*C*) Bucky chest roentgenogram made on same date as *B* shows widening of the mediastinal reflection behind the heart shadow at the left base. (*D*) Autopsy specimen of the esophagogastric junction shows multiple deep ulcers.

drug therapy. In 1933 Cooke[3] reported subserous intestinal hemorrhages in one and a perforated appendix in another child in association with leukemic infiltrates. Patton and Sommers[11] state that debility is a major factor in allowing bacteria or fungi to invade tissues and to progress to ulcers.

In the extensive literature on the related problem of "pseudomembranous enterocolitis" one finds many other possible causes listed. These include *Staphylococcus aureus* infection,[8,12] vascular stasis,[9] stagnation of feces proximal to obstructing tumors,[5] bacterial invasion secondary to

hemorrhagic necrosis,[10,14] clostridium welchii toxin,[6] and shock.[4] Several of these factors may have been acting concomitantly in some of our patients, whereas others may have played no part at all.

Our review of this series of autopsy cases often revealed roentgenographic clues to the localization of necrotizing enteropathy when roentgenograms were made during the acute phase of the disease. Roentegnograms made more than 1 to 2 weeks prior to surgery or autopsy were of no help in localizing pathology. This may be due to the fact that the disease process progresses rapidly in patients approaching a terminal state. In perforations of the gastrointestinal tract, particularly of the terminal ileum or right colon, roentgen findings guided a decision to early operative intervention, which in some cases prolonged life. Along with other clinical signs, roentgenograms may offer ancillary guidance to the need for a change in the therapeutic regimen.

SUMMARY

Seventy-two cases of necrotizing enteropathy encountered in autopsies performed on leukemia and lymphoma patients are reviewed.

The lesions can be classified into 4 major groups based on pathogenesis. The roentgenographic findings are less specific, presenting a variable pattern of ileus and incomplete or complete small or large bowel obstruction.

Awareness by the radiologist, however, that these findings may be the earliest sign of a necrotizing enteric process will alert the clinician towards a change, perhaps lifesaving, in the patient's therapeutic regimen.

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INTESTINAL STENOSIS FOLLOWING RADIATION THERAPY*

A ROENTGENOLOGIC-PATHOLOGIC STUDY

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IN AN effort to increase the survival rate of persons with malignancies treated by radiotherapeutic means, the radiation therapist has always been faced with the problem of severe and permanent damage to the surrounding normal tissues. With regard to the large bowel and more specifically to the sigmoid and rectal areas, the radiotherapist has long been aware of the late complications that may occur if the tolerance levels of the normal tissues are exceeded. In 1935, Jones[9] referred to stricture of the intestine, secondary to radium and roentgen ray therapy for carcinoma of the cervix, as a rather new clinical entity. Only a few reports of this complication had appeared in the literature up to 1935. In 1944, McIntosh and Hutton[11] stated that enough cases of bowel damage had been reported to establish radiation stricture of the intestine as a definite clinical entity. Requarth and Roberts[13] noted that the modern trend toward higher radiation doses has led to an increase in the complications of therapy. He also pointed out that a certain per cent of these complications must be accepted if the cure rate is to be at its maximum level. This concept of acceptable risk is recognized in many aspects of medicine, especially in the treatment of neoplastic diseases. In dealing with malignant neoplasms, extreme measures are often needed to eradicate an otherwise fatal disease. Complications of any mode of therapy must be evaluated and balanced against the over-all results.

The purpose of this paper is to present and correlate the roentgenographic and pathologic features of radiation stenosis of the bowel. This will secondarily serve to review the entire problem. As many authors have pointed out, radiation stenosis must be kept in mind since the symptoms of this condition may closely mimic those of recurrent or persistent cancer;[1,9,16] however, Ritvo and Shauffer[14] state that the symptoms produced are only rarely due to the original lesion. If the patient is to be treated properly, the correct diagnosis must be established. In most cases this can be accomplished by doing a barium enema study when indicated by the patient's signs and symptoms.

CLINICAL SYMPTOMS AND INCIDENCE

The frequency of stenosis of the intestine following irradiation varies from 1 per cent to 12 per cent of patients treated.[6,10,13] Most examples of this complication have occurred following therapy for carcinoma of the cervix and endometrium.[1,18]

The clinical features of radiation stenosis of the large bowel have been well described by Jones,[9] Spachman,[16] and others. Briefly, the symptoms of this late reaction to radiation therapy usually begin with abdominal cramping and frequent small liquid stools which may contain blood and mucus. Progressive constipation and tenesmus are frequent symptoms. Later the symptoms of obstruction or perforation may occur, occasionally with dramatic suddenness. Colcock and Hume[4] describe the sudden onset of peritonitis after radiation therapy and state that these cases should be promptly

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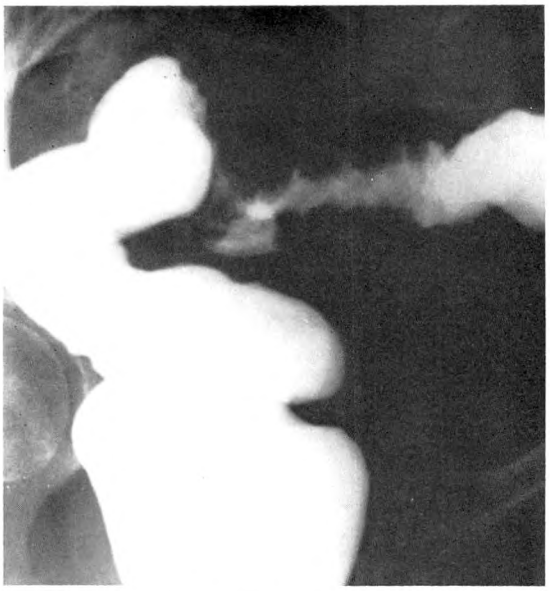


FIG. 1. Case VIII. Sigmoid colon reveals long (8 cm.) segment with distorted "saw-toothed" mucosa, broadened folds and ulceration. Gradual tapering on both sides of the ulcer is seen. W.U. Ill. No. 59-3435.

investigated by laparotomy because of the likelihood of perforation. Obstruction is rarely the first manifestation of stenosis. The symptoms may begin any time from several months up to many years after the completion of therapy.

In this paper 9 cases of intestinal stenosis following radiation therapy are briefly summarized. Four of the cases were treated for carcinoma of the cervix, 2 for carcinoma of the endometrium, and 1 each for carcinoma of the ovary, carcinoma of the vagina, and lymphosarcoma of the stomach. These cases were selected on the basis of good roentgenographic and pathologic correlation. No attempt has been made to arrive at an incidence rate of this complication at Barnes Hospital. Some of the patients had radiation therapy at hospitals other than Barnes Hospital; data on the total dose given are not available for these patients.

A summary of some of the pertinent data can be found in Table 1. It is noted that the time interval between treatment and the onset of bowel symptoms ranged from three months to four years. Jones[9] gave a range of eight months to eight years in his report. In Case II it had been assumed that the patient's symptoms were from a persistence of the lymphosarcoma. Thus, as stated above, the need for a correct diagnosis before re-treatment is emphasized and should be obtained whenever possible.

The conservative and, if necessary, the surgical management of the late complications of radiation damage of the bowel has been well discussed elsewhere and will not be detailed here.[1,4,13] It should be pointed out, however, that a temporary colostomy without resection of the affected segment may be sufficient, as the stenosis may not be permanent.[16] This is because edema and infection may subside and the remaining scar tissue and fibrosis alone may not cause further symptoms.

CASE SUMMARIES

CASE I. H.P., a fifty year old female, developed a sudden increase in menstrual flow. Dilatation and curettage and biopsy revealed adenocarcinoma of the endometrium. She was treated in November, 1948. In March of 1951 she developed constipation and abdominal pain which were unrelieved by medical management. Later in 1951, she underwent a left colon resection at which time the pathologic sections revealed radiation effect and no evidence of tumor.

Case II. E.S., a fifty-five year old male, reported a six months' history of vague epigastric distress and weight loss. A gastric fill-up revealed an infiltrating lesion along the lesser curvature of the stomach. In 1949, the patient underwent a subtotal gastrectomy with a postoperative pathologic diagnosis of lymphosarcoma. In June, 1950, and again in July, 1954, he was given roentgen ray therapy. Later in 1954, he developed left upper quadrant pain and fever. A barium enema examination revealed narrowing of the distal transverse colon (Fig. 10). This was assumed to be a recurrence of his disease but subsequent symptoms necessitated resection of a segment of colon. A pathologic diagnosis of radiation effect without evidence of tumor was made.

Case III. T.H., a forty-two year old female,

TABLE I

SUMMARY OF CASES

Case	Diagnosis	Therapy		Post Therapy Symptoms	Time Interval from Treatment to Symptoms	Pathologic Findings
		Type	Estimated Total Dose to Intestine			
I. H.P.	Carcinoma of endometrium	Radium and external roentgen ray therapy	Unknown	Constipation and tenesmus	2 yr.	Sigmoid: edema and fibrosis in submucosa and serosa. Hypertrophy of muscularis with general chronic inflammation. No foam cells
II. E.S.	Lymphosarcoma of stomach	External roentgen ray therapy (200 kv.)	2,730 r–1950 2,230 r–1954	Left upper quadrant pain with mass (fecal impaction)	4 yr.	Distal transverse colon: 1.5 cm. stenotic area of 0.5 cm. diameter. Mucosa eroded with acute ulcer penetrating into muscularis, but no perforation. No foam cells
III. T.H.	LON I carcinoma of cervix	Radium and external roentgen ray therapy	Unknown	Lower abdominal cramping pain and back pain	2 yr.	Sigmoid: 5 mm. ulcer with perforation present; 3 cm. of edema and narrowing on both sides of ulcer. Fibrosis of submucosa, with fat necrosis in mesentery. Foam cells present
IV. C.O.	Carcinoma of endometrium	Surgery, betatron radiation and intraperitoneal Au^{198} instillation after discovery of mass and peritoneal implants	6,750 r in 8 wk. (interrupted)	Abdominal cramps and bloody diarrhea	4 mo.	Sigmoid and ileum: narrowing of both with small ulcers in ileum. Hypertrophy of muscularis, and moderate submucosal edema. No foam cells
V. C.L.	Carcinoma of vagina	Betatron radiation and radium	6,500 r in 6 wk.	Abdominal pain, diarrhea with mucus and blood	9 mo.	Sigmoid: edema, fibrosis with 3 cm. ulcer, extreme submucosal perforation. Other skip ulcers present. Foam cells present
VI. F.G.	LON II carcinoma of cervix	Radium and parametrial Au^{198} injection	5,300 r in 6 wk. (probe reading)	Increased constipation	3 mo.	Sigmoid: stenotic area 3 cm. long with 5 mm. ulcer. Surrounding edema and fibrosis. Necrosis of inner muscularis. Foam cells present
VII. H.S.	LON II carcinoma of cervix	Radium and parametrial Au^{198} injection	5,300 r in 4 wk. (probe reading)	Rectal pain, proctitis with rectal bleeding	6 mo.	Rectosigmoid: 2 cm. constricted area with superficial ulceration. Marked edema 4 cm. to either side of ulcer. Usual fibrosis seen. Foam cells present
VIII. M.S.	LON III carcinoma of cervix	Radium and parametrial Au^{198} injection	5,940 r in 4 wk.	Abdominal cramps with diarrhea containing mucus and blood	7 mo.	Sigmoid: 2 cm. of stenosis with perforated ulcer. Marked edema. Bowel kinked at site of ulcer. Foam cells present
IX. P.A.	Carcinoma of ovary	External roentgen ray therapy, and intraperitoneal Au^{198} instillation	Unknown	Rectal and later also vaginal bleeding with pain	4 mo.	Sigmoid: large (5×2 cm.) ulcer with perforation into vagina. Marked surrounding edema. Necrosis of inner muscularis. Foam cells present



Fig. 2. Case VII. Short segment of sigmoid showing lack of distensibility, but no ulceration. W.U. Ill. No. 59-3440.

had a biopsy of the cervix and a pelvic examination which led to a diagnosis of carcinoma of the cervix, Stage LON I. The patient was treated with radium and external roentgen ray therapy.

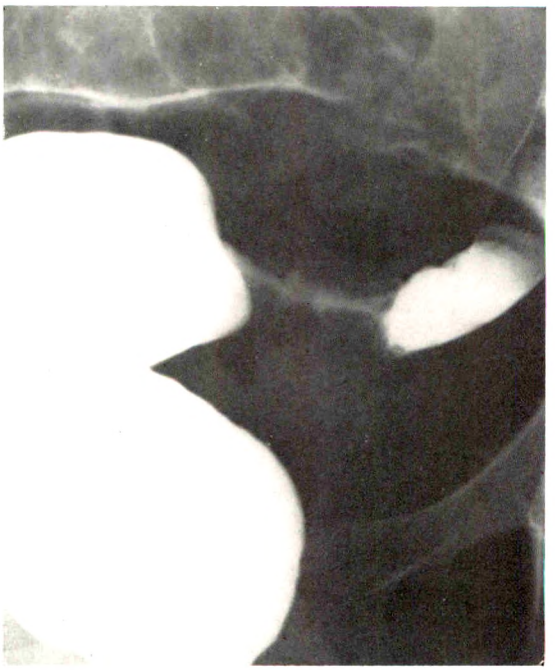


Fig. 3. Case III. Sigmoid stenosis 8 cm. in length. No obstruction to orthograde flow of barium was present, however. W.U. Ill. No. 59-3436.

Two years later severe lower abdominal cramping pain occurred. A barium enema examination revealed stenosis of a segment of the sigmoid colon (Fig. 3). The patient subsequently had a resection of the affected segment and the specimen showed radiation effect (Fig. 7).

Case IV. C.O., a forty-three year old female, gave a long history of menstrual complaints and a diagnosis of carcinoma of the endometrium was made in Topeka, Kansas. She was treated by hysterectomy. Six months later she was referred to Barnes Hospital because of "recurrence." The patient had extension of tumor into the vagina. Abdominal exploration revealed the patient to be inoperable even for pelvic exenteration. She was treated with the betatron unit and was later given intraperitoneal Au^{198} for ascites. She developed symptoms of lower intestinal obstruction (Fig. 11) necessitating resection of the sigmoid. Both radiation effect and metastatic carcinoma were found. The patient eventually died with extensive generalized metastases.

Case V. C.L., a forty-seven year old female, developed a lower abdominal mass. This mass



Fig. 4. Case V. Five centimeter long stenotic segment of the sigmoid. Ulceration in several areas can be seen. Slight tapering proximally is present. W.U. Ill. No. 59-3428.

was noted to involve the vagina. A biopsy diagnosis of epidermoid carcinoma probably originating in the vagina was made. The bladder, urethra, and ureters were proved to be invaded by carcinoma. The patient was treated with the betatron unit and radium implantation into the vagina. She subsequently developed bloody stools; a barium enema study revealed poor distensibility of the sigmoid and rectum (Fig. 4). The patient underwent pelvic exenteration. The bowel lesion showed only radiation effect (Fig. 9 and 13).

Case vi. F.G., a seventy-one year old female, with Stage LON II carcinoma of the cervix was treated with two radium implants and parametrial radioactive gold injections. She later developed progressive constipation. A barium enema revealed a stenosed area of the sigmoid colon (Fig. 5). A resection was performed and only radiation effect was found (Fig. 12 and 15).

Case vii. H.S., a thirty year old female, was diagnosed as having a Stage LON II carcinoma of the cervix. She was treated with radium implants and parametrial radioactive gold injections. Six months after therapy rectal pain and bleeding appeared; barium enema examination revealed a sigmoid stricture (Fig. 2). Resection and a transverse colostomy were performed. Examination of the specimen revealed radiation effect (Fig. 8 and 14).



Fig. 5. Case vi. Severe obstruction to retrograde flow with tapering of distal end of the stenosed area. W.U. Ill. No. 59-3439.

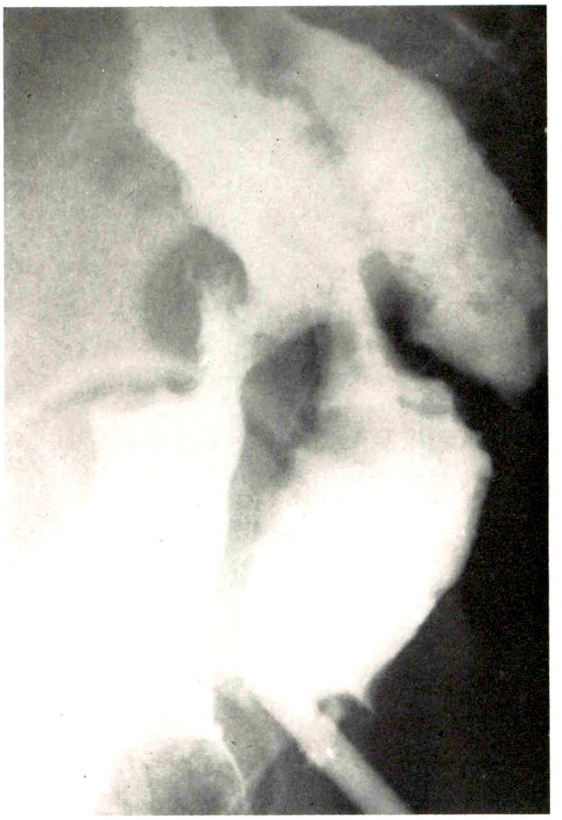


Fig 6. Case ix. Perforation of the sigmoid with a rectovaginal fistula and abscess formation. W.U. Ill. No. 59-3437.

Case viii. M.S., a forty-three year old female with a Stage LON III carcinoma of the cervix, was treated with radium and parametrial radioactive gold injections. This was followed in one month by a panhysterectomy including a lymph node dissection. Seven months later she developed low abdominal cramping pain with diarrhea that was occasionally bloody. A barium enema study revealed a sigmoid stenosis (Fig. 1) which was resected. There was no evidence of tumor and the stenosis was found to be the result of the radiation therapy (Fig. 16 and 17).

Case ix. P.A., a twenty-seven year old female, was diagnosed as having an ovarian carcinoma and was treated with an unknown amount of roentgen ray therapy. She was seen at Barnes Hospital with pelvic nodules and ascites and was treated with radium and intraperitoneal Au^{198}. She subsequently developed diarrhea with blood and mucus followed by severe rectal and vaginal bleeding. A barium

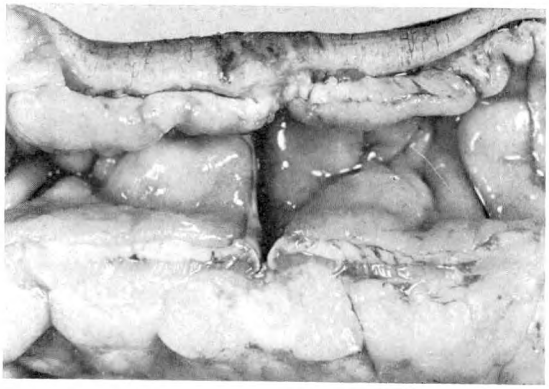


FIG. 7. Case III. Segment of sigmoid shows a narrow, sharply circumscribed ulcer with necrosis of the muscularis. Perforation was present. The adjacent mucosa and submucosa are edematous and contribute to the narrowing of the bowel lumen. W.U. Ill. No. 58-5374.

enema examination revealed ulceration and perforation of the sigmoid colon with a recto-vaginal fistula (Fig. 6). A resection of the sigmoid and a transverse colostomy were performed. Metastases in the left ovary were found but bowel changes were those of radiation effect.

ROENTGEN FINDINGS

The roentgen findings in stenosis of the large bowel are best demonstrated by a barium enema examination, which is essential in establishing the diagnosis.[14] While the clinical picture of postradiation stenosis



FIG. 8. Case VII. A 2 cm. area of stenosis with ulceration in the rectosigmoid. Edema and hyperemia of the mucosa on either side of the ulcer are present. The plicae semilunares are effaced. W.U. Ill. No. 58-5374.



FIG. 9. Case V. The stenotic zone of the sigmoid is occupied by a distinctly outlined ulcer measuring 3 cm. in its greatest diameter. Islands of mucosa are present in the hemorrhagic base of the ulcer. The intact muscularis, submucosal fibrosis, and mucosal edema are evident. W.U. Ill. No. 57-447. (Reproduced with permission from Moss, W.T.: Therapeutic Radiology, St. Louis, 1959, The C.V. Mosby Co.)

of the bowel may mimic recurrent cancer, the findings of the barium enema examination usually do not. The sigmoid colon is the most common segment to be involved, since most cases occur following the treatment of carcinoma of the cervix or corpus uteri.[11] Both the mucosal pattern as well as the over-all contour of the bowel is affected. In some cases in which some distensibility of the bowel remains, there is noted the "saw-toothed" appearance of the mucosa due to submucosal edema and fibrosis which broadens the plicae (Fig. 1). In the experi-



FIG. 10. Case II. This segment of transverse colon contains a long, stenotic area. The bowel lumen at this point measured 0.5 cm. in diameter. Mucosal edema and serosal scarring are present. W.U. Ill. No. 54-4791.

ence of the authors, while the involved segment may be short (Fig. 2), it is usually longer than one would expect with carcinoma. In Figure 3 the length of the bowel involved as measured on the roentgenogram was about 8 cm. The relatively long length of the bowel which is involved may be due in part to the fact that the lumen of the bowel and its distensibility will be limited not only at the site of actual stricture, but proximally and distally to the stricture as well. This is because of the presence of edema.

A rather constant roentgenographic finding in radiation stenosis is the lack of sharp demarcation between normal and abnormal segments of bowel. In this and other respects, the roentgenographic appearance is somewhat like that of diverticulitis. A more gradual tapering than is seen with carcinoma is almost always present (Fig. 4). Although there may be an abrupt change at the site of severe stenosis, there is often a tapering on both sides of the severely stenotic area. The usual finding in a carcinoma is an abrupt change from normal to abnormal bowel.

Ulceration was common in our cases. Seven of the 9 cases had some degree of ulceration in the constricted areas as can be seen in Figures 1 and 4. In some cases multiple ulcers may be present which are demonstrable by barium enema examination.

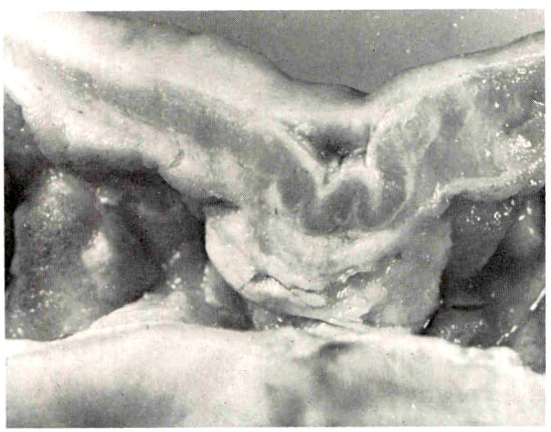


Fig. 11. Case IV. An extremely stenotic part of the sigmoid without ulceration. The muscularis is intact but thickened. Submucosal and serosal fibrosis are present. A segment of ileum contained scattered ulcers and serosal metastases. W.U. Ill. No. 59-599.



Fig. 12. Case VI. A stenotic area, 3 cm. in length, in the sigmoid colon. A small ulcer was present in this zone. Submucosal and mucosal edema have effaced the plicae semilunares. The mesentery is hyperemic and thickened. W.U. Ill. No. 56-4890.

Obstruction is usually a late development and may be obvious on routine erect and supine roentgenograms of the abdomen. Some degree of obstruction to retrograde flow of barium is common to all stages of this condition because of decreased distensibility and spasm. Complete obstruction to retrograde flow is not so common but is seen (Fig. 5). However, it must be remembered that there may be more obstruction in the orthograde direction than one might expect by observing the retrograde filling of the bowel during barium enema examination. Ritvo and Shauffer[14] stress that large enemas are not advisable and that multiple spot roentgenography offers the best method of demonstrating the lesion with cautious outlining of the involved segment. Filling of the entire bowel is thus somewhat superfluous and may lead to the serious difficulty of impaction of the barium above the lesion.

Perforation through a necrotic area occurs in severe cases, and this may be accompanied by abscess and fistula formation (Fig. 6). Where perforation is suspected or believed likely to have occurred, a water soluble medium rather than barium should be used in the contrast enema examination.

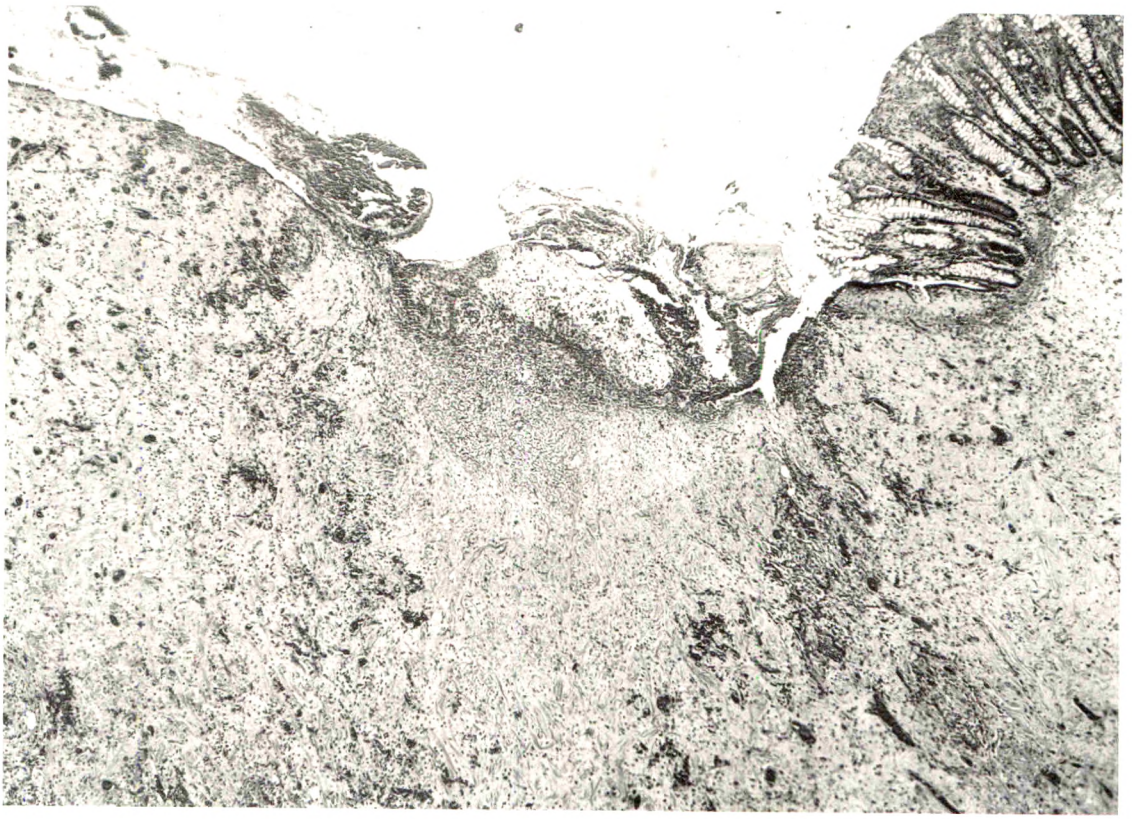


FIG. 13. Case v. An ulcer that is partially re-epithelized by a single layer of cells. The submucosa is fibrotic and richly vascular. W.U. Ill. No. 59-2778. (×47.)

PATHOLOGIC FINDINGS

Of our 9 cases, in 8 there was involvement of the rectum or sigmoid colon and in 1 of the transverse colon. Histologically and grossly, the alterations were quite similar regardless of the interval between the radiation therapy and the resection. In each specimen the stenotic zone was circumbscribed, short, and often kinked (Fig. 7). The length of the stenotic segment measured from 0.5 to 5 cm. with the majority 1.5 to 2 cm.

To either side of the stenosed part of the mucosa and submucosa, the bowel was thickened by edema and fibrosis for 3 to 4 cm. to cause erasement or broadening of the normal mucosal folds (Fig. 8 and 12). Ulcerations were observed in 7 of the constricted areas. The ulcers varied from 5 mm. to 5 cm. in diameter. Except for the specimen with the smallest ulcer, the entire or nearly the entire area was ulcerated. The edges of the ulcer were distinctly defined with only a slight amount of heaping of the mucosal edges (Fig. 9). Grossly, the lesions were not characteristic of carcinoma.

The wall of the bowel was thickened with the major part of the thickening due to edema and fibrosis of the mucosa, submucosa, and serosa. The muscularis appeared hypertrophied (Fig. 9 and 11) and remained intact except in areas of necrosis. Perforations were present in 4 of our specimens. Hyperemia and thickening of the mesentery and hyperemia of the serosa were common findings.

Microscopically, a constant feature was submucosal edema and fibrosis, the fibrosis being most notable near the ulcers. The fibrous tissue in the bed of the ulcers was poorly organized with prominent fibroblasts. In the collagenized portions the in-



Fig. 14. Case VII. Atrophy of the mucosa and hyperplasia of the surface epithelium are seen. Vascular dilatation is prominent. W.U. Ill. No. 59-2773A. (×155.)

dividual fibers were smudged, giving a homogeneous and acidophilic appearance. This peculiar alteration of the collagen fibers represents a fairly characteristic finding in radiation effect wherever it may occur.

Re-epithelization of the base of the ulcers may be present and consists of a single row of columnar cells (Fig. 13). Atrophy or disorganized hyperplasia may be seen in the mucosa adjacent to the ulcer (Fig. 14). Atrophy was not a common finding in our specimens. Sites of perforation were associated with ulcers and necrosis through the muscularis.

Degenerative alterations were noted in the muscularis of 7 of the 9 specimens. Most remarkably, the mid-zone of the muscu-

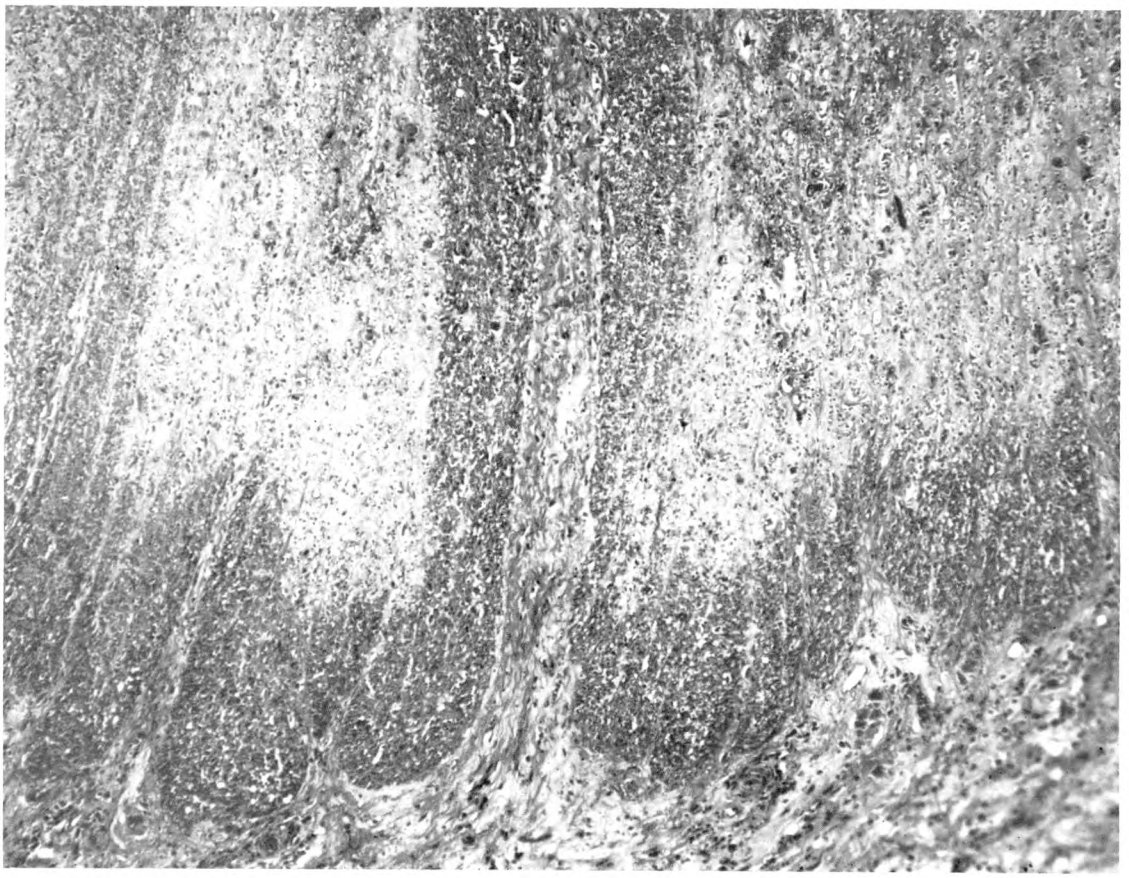


FIG. 15. Case VI. Necrosis of the inner muscular coat is seen. W.U. Ill. No. 59-2774A. (×140.)

laris was most severely affected. Not uncommonly, the outer longitudinal coat was spared. In only one instance did the outer muscular coat show vacuolar degeneration with no change of the inner coat. The histologic features noted in the muscularis were vacuolization of the muscle fibers, edema and acute necrosis. In what is apparently a healed phase, the muscle bundles are replaced by scar tissue (Fig. 15). An explanation for the distribution of the lesion in relation to the muscle coats is not apparent at this time. Except in areas of ulceration, the muscularis mucosae remained intact.

Vascular damage was spotty and, in general, confined to the grossly stenotic zone. The blood vessel modifications were among the most interesting findings that we observed. Vessels in all layers of the bowel wall and the mesentery were affected, but by no means all vessels. The vascular changes varied from endothelial proliferation and vacuolization to focal medial necrosis or smudging to complete thrombotic occlusion of small veins and arteries.

The most remarkable vascular alteration and one which may have some specificity in regards to radiation effect was the finding of collections of large foam cells directly beneath the intima and on the luminal side of the internal elastica. Most often small arteries were involved, but, in occasional medium-sized vessels, this change was also noted (Fig. 16). The foam cells were often numerous enough to occlude the lumen of a vessel (Fig. 17). Only rarely were the foam cells accompanied by inflammatory cells. The walls of the vessels were not necessarily altered. These findings have been described previously by Sheehan.[15] Others have not mentioned them al-

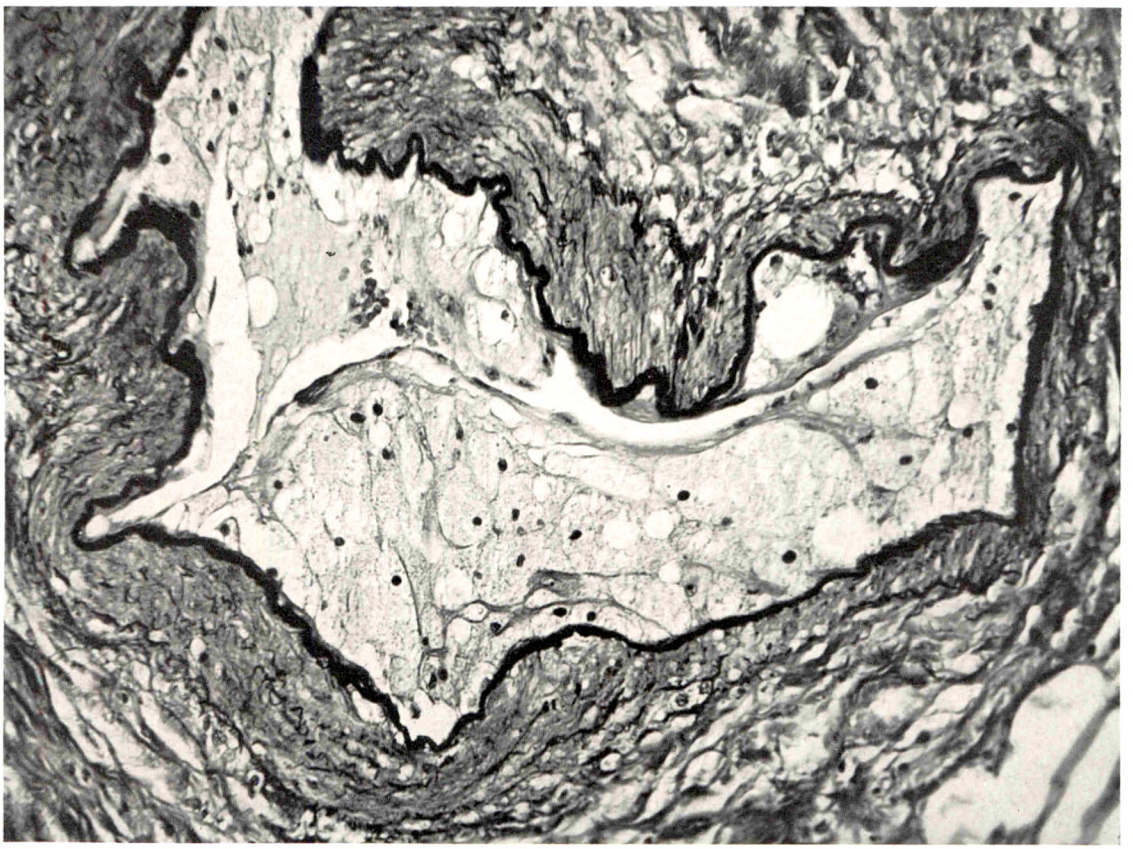


Fig. 16. Case VIII. Verhoeff-van Gieson stain accentuates the internal elastica. The foam cells are clearly shown to be subintimal. The media does not appear to be altered. The lumen is compromised. W.U. Ill. No. 59-2771A. (×275.)

though the importance of vascular damage in the genesis of the bowel wall changes is stressed. It is thought that the foam cells represent damaged endothelium in which there has been inbibition of lipids. An alternative is organized thrombus.

The serosa of the specimens is often thickened by fibrous tissue and may contain inflammatory cells. Two of the patients who had received parametrial injections of radioactive gold had gold particles in the serosa and mesentery. No particular importance could be attached to their presence in the way of morphologic changes except for possibly more serosal and mesenteric fibrosis.

DISCUSSION

The radiologic and pathologic features have been presented in some detail. From these discussions a number of correlative points can be made. It has been stated that the stenosed section, as seen on roentgenograms, measured from 3 to 8 cm. in length, while in the surgical specimens it ranged from 0.5 to 5 cm. This is due in part to a lack of distensibility of the edematous area of the bowel which was not actually stenosed. However, on barium enema studies this greater length appears to be involved. Furthermore, the actual length of the stricture in the surgical specimen probably represents what was originally a much greater length of bowel. Spratt *et al.*[17] exposed isolated segments of dog ileum, 5 cm. in length, to 4,000 r air dose in a single seance. In eight months marked contraction had occurred and in one instance only a 2 mm. scar remained from the original 5 cm. segment.

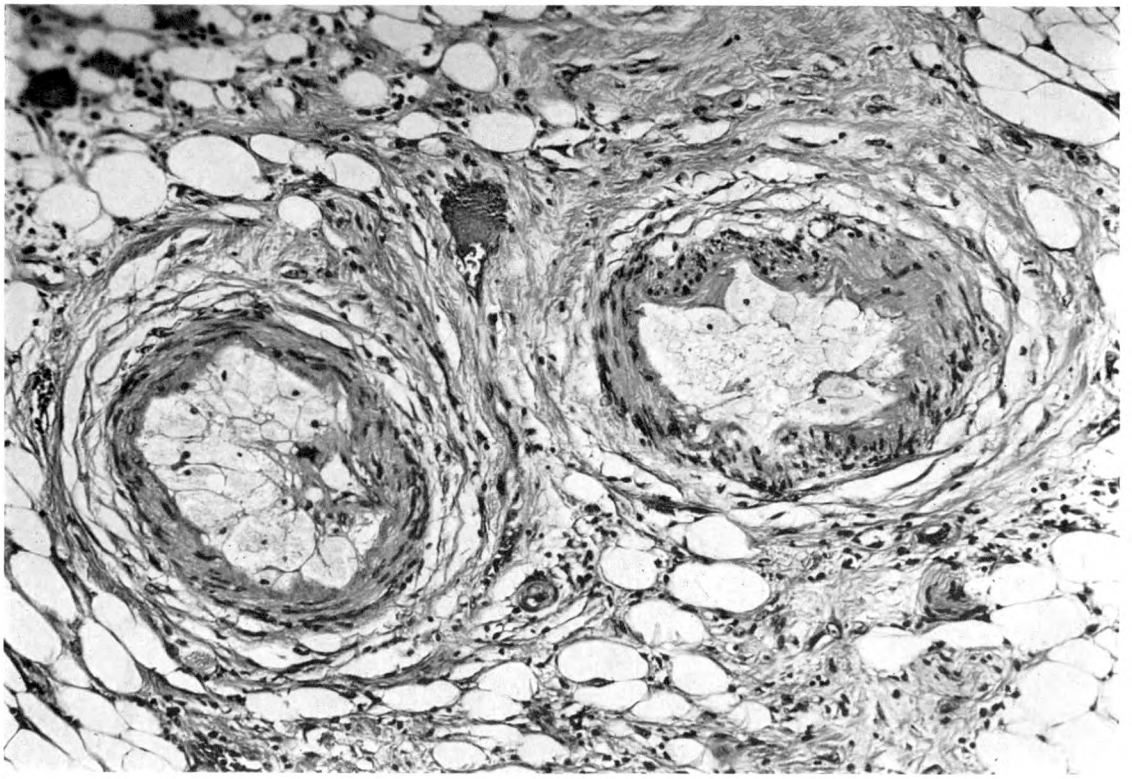


FIG. 17. Case VIII. Subintimal foam cells in two small mesenteric arteries. The lumina are nearly obliterated. W.U. Ill. No. 59-2772A. (×165.)

The edema and fibrosis which erase or broaden the normal folds have been demonstrated roentgenographically and pathologically (Fig. 1 and 8).

While it is not the primary purpose of this paper to evaluate the therapy of these cases, the doses given should be studied as an indication of the dose level needed to produce the condition of radiation stenosis. The first point to be examined is the tolerance levels of the bowel itself. Work on tolerance levels of normal bowel is complicated by the fact that such tolerance not only varies from patient to patient, but also with the fractionation, the irradiated volume, the quantity, and perhaps the quality of the radiation used.[12] In 1955, Brick[2] reported on the results of 100 patients treated with 1 mev. roentgen radiation to areas of the abdomen for the treatment of lymph nodes in cases of testicular tumors. He concluded that the safe maximum dose for the stomach and small bowel was about 4,000 r and that the colon would tolerate about 4,500 r. With these doses given over a fifty to sixty day period, there were usually no serious temporary reactions and only rare late sequelae.

That there is a wide variation and individual susceptibility is well known. Cathie[3] reported 2 fatalities from small bowel perforations after only 1,500 r. However, Gray and Kottmeier[8] concluded that a dose of more than 5,000 r or 6,000 total r appears to carry a high risk of injury. In 3 of our cases in which the total dose to the rectum was known (as measured by a probe scintillation counter), the dose was greater than 5,000 gamma roentgens.

Fletcher *et al.*[7] have reviewed many clinical data on the tolerance of both the bladder and rectum and have concluded that: (1) "There is no evidence of absolute levels for the radiation tolerance of the bladder and rectum. Radium therapy should not be set by using theoretical blad-

der and rectum doses as the limiting criteria" and (2) "There is a wide margin of dose level within which an increase in the complications will occur." Thus, the question of tolerance for each individual patient is a difficult one.

When treating for cure of a cancer, 5,000 r or more to the rectum and sigmoid is often exceeded in order to obtain the maximum number of cures. Thus, the need for better dosimetry in terms of total dose received by the sigmoid and rectum becomes important if for no other reason than a predictive value of possible future complications. The recent use of a probe type scintillation counter to measure the dose delivered to the rectum in cases of carcinoma treated with radium is a step forward. However, as noted here and elsewhere, the most common site of stricture is not in the rectum but actually higher, in the rectosigmoid area. In 2 of the cases of carcinoma of the cervix presented (Cases VII and VIII), superimposition of anteroposterior and lateral roentgenograms of the radium and anteroposterior and lateral roentgenograms of later barium enema studies revealed the almost contiguous position of the affected loop of bowel to the top load of radium in the uterine tandem portion of the radium applicator. Therefore, it is possible that a longer and curved type of probe scintillation counter will give a more accurate location of the highest rectal and rectosigmoid exposures during the radium application.

SUMMARY

1. The clinical entity of radiation stenosis of the bowel is briefly reviewed. Nine new cases are added to the literature.

2. The dangers of mistaking this entity for persistent cancer is noted. The radiologist has jurisdiction over the essential means by which the diagnosis can be made—namely, the barium enema examination.

3. The roentgenographic and pathologic features are presented.

4. The presence of foam cells in the subintimal areas of small arteries is mentioned as being a possible specific finding in vascular damage from radiation.

5. A longer and curved probe scintillation counter rather than those currently in use would give a more accurate location and reading of the highest rectal and sigmoid dose delivered by the radium applicator in the treatment of carcinoma of the cervix.

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RADIATION RESPONSE OF CARCINOID OF THE RECTUM*

A CASE REPORT

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"CARCINOIDS of the large bowel are most frequently found in the cecal region and in the rectum; those in the rectum are usually diagnosed and treated early."[1] After the first report of a rectal carcinoid in 1912 by Saltykow,[11] twenty-one years elapsed before Brunschwig,[3] in 1933, reported a second case. In 1957, compiling the reports of rectal carcinoid in the world literature, Lamphier and Ehrlich[7] added 214 cases.

Since surgical procedures have been universally accepted as the treatment of choice for this disease, there has been little contributed to the literature regarding the radiation response of carcinoid of the rectum. Two patients who had radiation therapy of the primary tumor were reported by Root, Leddy, and MacDonald.[9] In one of these, treatment with radon seed and external roentgen therapy was given postoperatively. The patient remained free of disease until metastatic lesions appeared twenty-four years later. How much the radiation alone contributed to the length of survival cannot be assessed. The other patient had a recurrent rectal carcinoid treated with cobalt teletherapy. Each of two posterior oblique fields received 2,250 r, but no change resulted in the size of the rectal mass.

Ellis[4] reported a rectal carcinoid that was locally resected and treated postoperatively with radon gold seeds and external medium voltage roentgen therapy. The interstitial dosage was calculated at 1,173 millicurie hours. In twenty-nine days, 2,200 r had been delivered to each of two fields by external roentgen therapy. Six years later metastatic growths in the liver were evident, although no abnormalities were noted on proctoscopic examination. The patient died thirteen years after the initial surgical resection and the postmortem examination showed a 3 cm. carcinoid in the rectum.

Evidence indicates that metastatic lesions from carcinoids, other than rectal, respond to irradiation if the primary lesion had been removed.[2,5,6,8] Roth[10] observed definite response when treating cutaneous metastatic growths from primary rectal carcinoid. Large doses of roentgen rays, 2,500 r in air in one day, were needed to cause disappearance of the skin lesions.

The following observation supplements the meager literature on radiation treatment of primary rectal carcinoids.

REPORT OF A CASE

A sixty-eight year old woman was admitted to the University of California Hospital, San Francisco, on May 31, 1960. In the preceding six weeks she had had recurrent anorexia and upper abdominal and epigastric pain. During this period she had lost 20 pounds. She had noted no change in bowel habits nor abnormal appearing stools. She had not had flushing or cardiorespiratory difficulty. In 1956 she had undergone cholecystectomy and rectal polypectomy.

On physical examination, the blood pressure was 140/98 and the pulse rate was 80 per minute and regular. An enlarged liver, extending to the right iliac crest, was firm, nodular, and nontender to palpation. Rectal examination showed a nonulcerated mass measuring approximately 2 by 2 cm., extending upward about 4 cm. into

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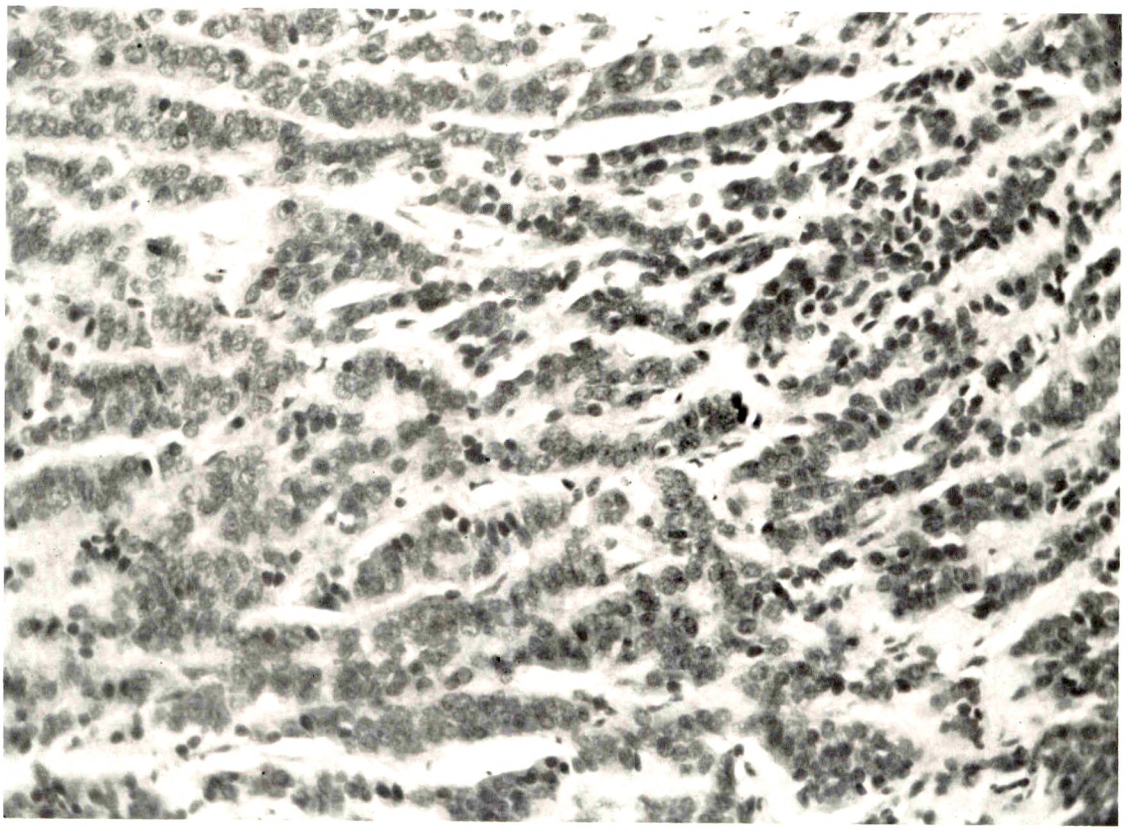


FIG. 1. Photomicrograph of original biopsy specimen of rectum (high power).



FIG. 2. Gross specimen at autopsy. Arrow points to tumor; hemostats on the skin surface.

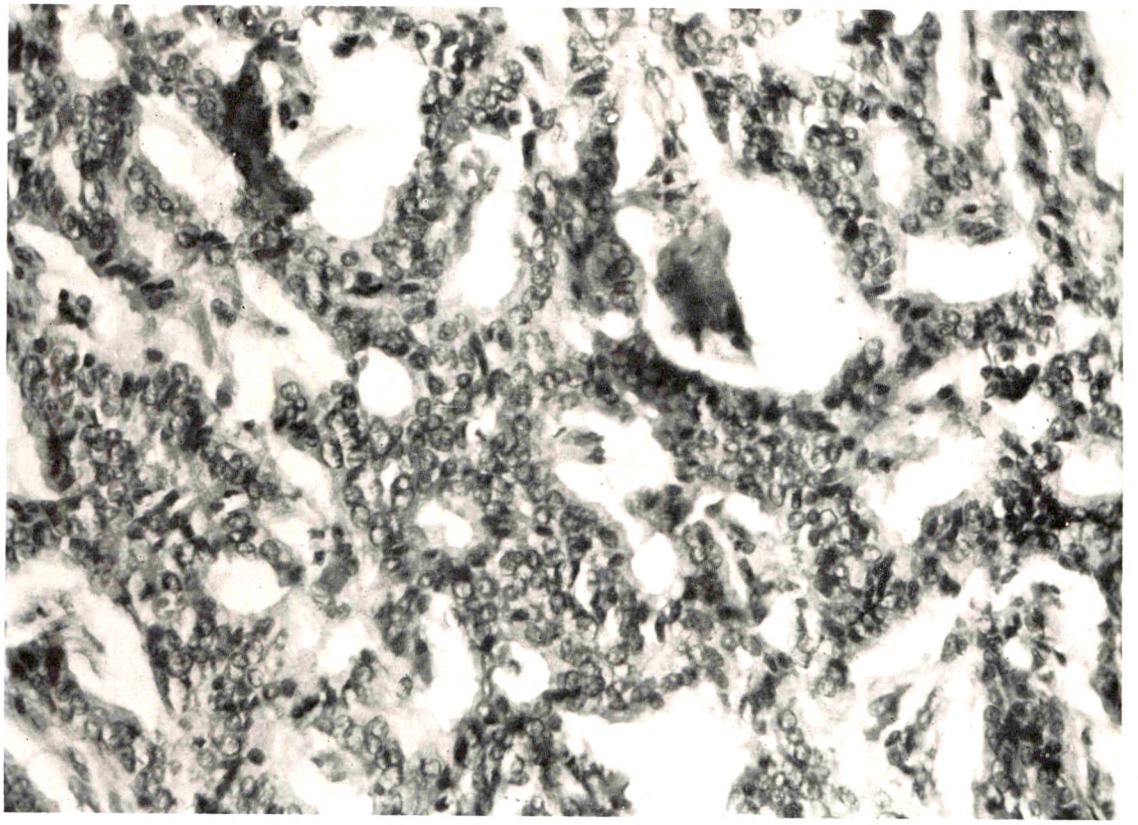


FIG. 3. Photomicrograph of tumor at autopsy (high power).

the left lateral rectum. On proctoscopy only an intact rectal mucosa was recorded. The results of laboratory studies showed a prothrombin time of 49 per cent, bromsulphalein of 25 per cent, and albumin-globulin ratio normal. The chest findings were within normal limits.

On exploratory laparotomy, June 6, 1960, an enlarged nodular liver with metastatic involvement was grossly obvious. Lesions were excised for biopsy and through a perianal skin incision a biopsy specimen was also obtained from the rectal mass. Because of the metastatic growths of the liver and location of the rectal tumor, no further operative procedure was performed. The pathologist reported a malignant carcinoid (argentaffin carcinoma) of the rectum with metastasis to the liver (Fig. 1).

On June 16, 1960, supervoltage roentgen therapy was initiated to the rectal mass through a 6 by 6 cm. left perianal field, using 1 mev. irradiation, 3 ma., no added filtration, half value layer 3.2 mm. Pb, and a focal skin distance of 70 cm. The perianal incision was slightly separated and appeared infected. A daily skin dose of 100 r was increased after 8 treatments (800 r/skin) to 150 r/skin daily. The induration about the incision was decreased at this time and the inflammation of the incision reduced. The rectal mass was less indurated and more discrete, probably because of the reduced inflammation. Its size, however, had not changed appreciably. From this time until completion of roentgen therapy, when 3,800 r/skin had been administered in a total treatment time of thirty-eight days, the mass had not changed.

An examination two weeks after completion of roentgen therapy showed no further change in the rectal tumor. Enlargement of the liver continued and on August 28, 1960, the patient died of her disease while in a hepatic coma.

On postmortem examination a submucosal mass was seen above the pectate line on the left posterior rectal wall measuring 1.8 cm. in diameter and surrounded by dense fibrosis (Fig. 2). The microscopic examination of cut sections from this mass revealed argentaffin carcinoma (carcinoid) (Fig. 3), similar to the original biopsy and without any evidence of radiation effect. Many abdominal lymph nodes were in-

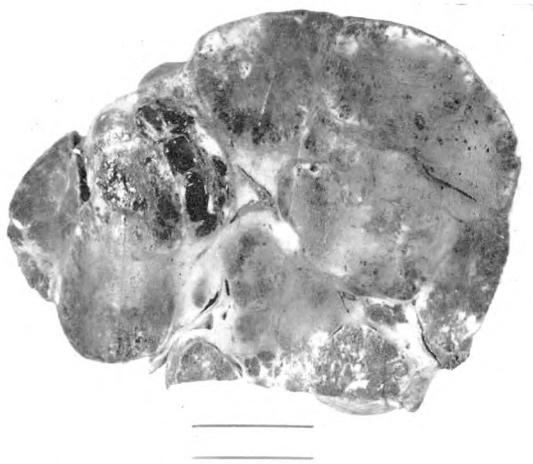


FIG. 4. Liver with metastatic nodules.

volved. The liver, weighing 1,800 gm., contained tumors measuring up to 15 cm. in diameter that were identified as carcinoid (Fig. 4). There was also microscopic evidence of pulmonary metastasis.

SUMMARY

A carcinoid of the rectum was treated with supervoltage roentgen therapy with a dose of 3,800 r/skin in thirty-eight days. Reduction in the induration surrounding the rectal mass early after starting therapy was attributed to the anti-inflammatory effect of the roentgen rays. Clinically and histologically, the rectal tumor showed no response to the radiation administered in this dose range.

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EPIDERMOID CARCINOMA OF THE CERVIX*

ORTHOVOLTAGE AND SUPERVOLTAGE IRRADIATION

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THE purpose of this paper is to compare the results obtained in carcinoma of the cervix by the same clinicians before and after the advent of supervoltage radiation therapy.

REVIEW

During the entire 65 year history of radiology, carcinoma of the cervix has been a major problem, causing much thought and effort on the part of radiation therapists and gynecologists. Nevertheless, unless supervoltage irradiation proves to be an advance, no really major innovation in the radiation treatment of this disease has been developed since the 1920's, when the principles of the combined use of intracavitary radium and external irradiation were laid down. Of great importance has been the indoctrination of radiologists into the value of accurate dosage determinations—a process to which contributions have been made by many scientists but outstandingly by Tod and Meredith.[9] Of related and equal importance has been the relatively recent emphasis on the value of individualizing treatment, again a subject discussed by many but notably by Kottmeier.[6]

Irradiation with the employment of an intravaginal cone has been a useful development, and there also have been many refinements and modifications in treatment planning, technique, and equipment.

Currently, attention is being given to the possibility of treating carcinoma of the cervix by supervoltage irradiation only. As pointed out by Mellor,[8] who has reported good results in a group of 17 patients so treated, when supervoltage irradiation is used alone, it is possible to deliver homogeneously an adequate dose to the primary lesion, to the areas into which direct spread can be expected, and to the pelvic lymphatics draining the cervix, simultaneously. The entire treatment can be given without hospitalization or anesthesia, the discomfort of the intracavitary application of radium is eliminated, the radiation hazards involved in handling radium are avoided, the patients' constitutional symptoms are minimized, and bladder and rectal complications are sharply reduced. However, a large scale evaluation of long term results is not yet possible.

In fact, a large scale comparison of long term results when orthovoltage irradiation is used in combination with intracavitary radium and when supervoltage irradiation is used in combination with intracavitary radium cannot yet be made.

In 1955, Burkell and Watson[1] described their experience at the Saskatoon Cancer Clinic. With orthovoltage irradiation, they used eight portals through which they were able to build up a tissue dose of 2,250 r to point B, while with supervoltage irradiation, using two pairs of directly opposing portals, they could increase the dose at point B to 3,250 r. They gave no statistical analysis of their results.

In 1957, Guttmann[5] reported figures from the Francis Delafield Hospital, New York, comparing three groups of patients—301 treated by 250 kv. external irradiation, intravaginal cone therapy and radium; 40, classified as Stage I and II, treated by 2 mv. external irradiation and radium; and 52, classified as Stage III and IV, treated by 2 mv. roentgen or cobalt 60 irradiation only. In the second and third groups, so few had been followed for five years that survival rates could not be determined, but Gutt-

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mann was favorably impressed by the greater immediate tolerance of supervoltage irradiation, noting that she was able to attack disease more aggressively with this modality while impairing the general condition of her patients to a lesser degree—"a contributing factor of utmost significance in the outcome of therapy." She also noted that postirradiation complications were fewer, and stressed the possibility for better control of disease because by means of supervoltage irradiation it was possible to deliver a homogeneous high dosage throughout the entire pelvis. Guttmann's average tissue dose delivered by orthovoltage irradiation was 2,700 r to which was added 1,140 r at 5 cm. depth through an intravaginal cone when supervoltage irradiation was combined with radium; 5,000 r was the average tissue dose delivered by supervoltage irradiation; and when supervoltage irradiation was used alone, the tissue dose ranged from 6,000–7,000 r.

In 1961, Decker and Van Herik[3] reported the results obtained at the Mayo Clinic in 1,300 patients with carcinoma of the cervix treated between 1940 and 1949. They stated that the patients given orthovoltage irradiation received 2,000–2,400 r in air to each of four pelvic portals whereas those given supervoltage irradiation received 3,500–3,700 r at the midplane, but they did not give separate results of the two groups.

In the 1960 Caldwell Lecture, Leucutia[7] reviewed, among other subjects, the evolution of radiation therapy of carcinoma of the cervix, but did not specifically evaluate the effect of the introduction of supervoltage irradiation. It would then seem to be appropriate and of interest to present the material which follows.

MATERIAL AND METHOD

In the five year period between September, 1953 and September, 1958, in a total of 371 patients with carcinoma of the cervix, there were 144 with epidermoid carcinoma of the cervix who received their primary treatment at the University of Virginia Medical Center and whose primary treatment consisted of orthovoltage irradiation only, cobalt 60 irradiation only, or radium therapy combined with orthovoltage or cobalt 60 irradiation.

The same gynecologic-radiologic team treated the patients, and the same intracavitary radium treatment plan was used throughout the five years. The cross arms of a Clark applicator were each loaded with 13 mg. of radium. In the intrauterine bar, one, two, or three 13 mg. capsules of radium were loaded, the number depending upon the depth of the uterus. Each side of a colpostat with flexible metallic connecting arms was also loaded with 13 mg. of radium. The inherent filtration in the cross bar was 1 mm. Pt, in the intrauterine bar 0.9 mm. Pt, and in the colpostat 1.5 mm. Pt. The usual precaution was observed of separating the bladder and rectum as much as possible from the inserted radium by packing. At the time of the insertion, readings were taken from dosimeters attached to probes in the rectum and bladder to aid in gamma roentgen dose determinations. Also postirradiation roentgenograms were obtained using contrast media in the rectum and bladder to demonstrate the position of the applicators, the rectum, and the bladder, and to determine the gamma roentgen dose to various points in the pelvis. The average dose at Point A, defined as that spot 2 cm. lateral and cephalad to the external os, was 6,000 r, the range was from 4,400 r to 6,900 r. The average dose at Point B, defined as that spot 2 cm. cephalad and 5 cm. lateral to the external os, was 1,500 r, and the range was from 1,100 r to 2,200 r. The dose at points 3 cm. anterior and posterior to the intersection of the cross bar and the uterine bar was from 3,000 r to 3,500 r. As demonstrated in the postirradiation roentgenograms obtained with contrast media in the bladder and rectum, the anterior point fell within the bladder and the posterior point within the rectum.

Between September, 1953 and September 1956, orthovoltage irradiation was used to supplement the intracavitary radium therapy. The half value layer was 2.0 mm. Cu

(250 kv.), and using the treatment plan described by Fletcher[4] in 1950, eight skin portals were employed in order to deliver an average dose of 3,500 r to Point B, raising the total dose there to an average of 5,000 r. However, the range was wide, 2,500 r to 4,500 r, due to variations in the size of the patients, and in the cutaneous, rectal, and constitutional tolerance; the rate of delivery was slow (about five weeks to give 3,500 r); and the dose through the pelvis was not homogeneous. In Stage IV cases and those in Stage III in which intracavitary radium could not be used, the external irradiation was given first. In many, this was followed by enough improvement for intracavitary radium to be given later.

Between September, 1956 and September 1958, cobalt 60 irradiation was used to supplement the intracavitary radium therapy. When the disease was classified as Stage I or II, two pairs of directly opposed, anterior and posterior, skin portals were used. The lower limit of the field was the level of the arcuate ligament, the upper limit was just above the level of the bifurcation of the abdominal aorta (the lower border of the fourth lumbar vertebra), the lateral margin was several centimeters beyond the lateral pelvic wall, and the fields were separated 7 cm. in the midline. Accuracy was ensured by a localization roentgenogram made with the patient in position on the treatment table. This plan was also used in a few early Stage III cases. By this means, the dose at Point B was raised to 6,000 r, which involved delivering a total dose of about 7,500 r at Point A. In most of the Stage III and in all Stage IV cases, the head of the cobalt 60 unit was rotated around the patient's pelvis. The upper and lower limits of the radiation field were as noted above, and a total dose of 5,500 r was delivered to the 100 per cent zone in five to six weeks.

In the patients who received the cobalt 60 irradiation, there were observed the advantages radiologists have learned to expect from supervoltage therapy. A larger dose was delivered in a relatively shorter time, the dose pattern through the pelvis was more homogeneous, and the side effects, constitutional and local, immediate and late, were sharply diminished.

In the earlier group which received orthovoltage irradiation, there were 68 patients. They were treated between September, 1953 and September, 1956, and their condition as of September, 1959 is being reported. The follow-up periods ranged from thirty-six to seventy-two months, with an average of fifty-six months. The cut-off date was selected in order to make this group comparable to the second group, which received cobalt 60 irradiation between September, 1956 and September, 1958. The condition of these 76 patients as of September, 1961 is being reported, with follow-up periods ranging from thirty-six to sixty months and averaging fifty-three months. The results are shown in Tables I, II, and III. It should be noted that in preparing these tables, patients lost to follow-up were presumed to have died of carcinoma of the cervix, and that carcinoma *in situ* was treated by radical hysterectomy.

DISCUSSION

Perhaps the first comment should be that statistics of this kind are affected by the way in which staging is decided. When there was doubt as to whether a patient should be classified as Stage I or Stage II, the gynecologists in the group who handled these patients placed her in Stage I; if the decision lay between Stage II and III, she was placed in Stage II, etc. Also, if a patient was classified as Stage I and found later to have distant metastases, she was not reclassified as Stage IV but was left in Stage I, etc.

In regard to the cases in Stage I, it was not surprising to find that the larger tissue dose made possible by cobalt 60 irradiation had a small effect upon the outcome. In these patients, thorough examination revealed no positive clinical evidence of extension beyond the cervix. The results suggest that clinical judgment was sound and that even microscopic extension was minimal. At this point in their development, almost

TABLE I

PATIENTS WHO RECEIVED 250 KV. IRRADIATION ONLY OR 250 KV. IRRADIATION PLUS RADIUM THERAPY

Stage	No. of Patients	Dead of Other Causes	Dead of Carcinoma of the Cervix	Alive with Demonstrable Disease	Alive with No Demonstrable Disease	Per Cent Alive with No Demonstrable Disease
I	29	3	4	1	21	72.4
II	20	1	10	3	6	30.0
III	9	0	9	0	0	0.0
IV	10	0	10	0	0	0.0
	68	4	33	4	27	

PATIENTS WHO RECEIVED Co^{60} IRRADIATION ONLY OR Co^{60} IRRADIATION PLUS RADIUM THERAPY

Stage	No. of Patients	Dead of Other Causes	Dead of Carcinoma of the Cervix	Alive with Demonstrable Disease	Alive with No Demonstrable Disease	Per Cent Alive with No Demonstrable Disease
I	28	1	3	1	23	82.0
II	25	2	7	2	14	56.0
III	8	0	5	1	2	25.0
IV	15	0	13	2	0	0.0
	76	3	28	6	39	

all of the carcinomas were confined to a volume of tissue within the zone receiving adequate radiation from the combination of intracavitary radium with either orthovoltage or cobalt 60 therapy. In a few, either the microscopic extension went beyond this zone or an unusually radioresistant tumor was encountered. However,

TABLE II

PATIENTS WHO RECEIVED 250 KV. IRRADIATION PLUS RADIUM THERAPY

Stage	No. of Patients	Alive with No Demonstrable Disease	Per Cent Alive with No Demonstrable Disease
I and II	49	27	55.0
All Stages	68	27	39.9

PATIENTS WHO RECEIVED Co^{60} IRRADIATION PLUS RADIUM THERAPY

Stage	No. of Patients	Alive with No Demonstrable Disease	Per Cent Alive with No Demonstrable Disease
I and II	53	37	70.0
All Stages	76	39	51.3

TABLE III

PATIENTS WHO RECEIVED 250 KV. IRRADIATION ONLY

Stage	No. of Patients	Alive	Survival Time (range)	Survival Time (average)
III	4	0		
IV	10	0		
	14	0	2 to 45 mo.	11.1 mo.

PATIENTS WHO RECEIVED Co^{60} IRRADIATION ONLY

Stage	No. of Patients	Alive	Survival Time (range)	Survival Time (average)
III	2	1		
IV	13	0		
	15	1 (37 mo.)	2 to 60 mo.	16.7 mo.

though the "alive with no demonstrable disease" figures were not appreciably affected, the relative freedom from side effects experienced by the patients receiving cobalt 60 irradiation represented a very real gain. The extra investment by the radiologists in treatment planning time was amply rewarded by the fact that there were fewer complications with which to deal. As for the patients, one must talk to those who have received courses of both orthovoltage and supervoltage irradiation to appreciate how real is this gain.

In our experience, it is in Stage II cases that supervoltage or cobalt 60 irradiation produces the greatest improvement. At this period in their development, when there is definite clinical evidence that the carcinomas have invaded to a moderate degree the upper vagina, a parametrium, the parametria, or all of these, the disease involves a volume of tissue all of which can be irradiated adequately by combining supervoltage irradiation and intracavitary radium. When orthovoltage rather than supervoltage irradiation is used, the average dose must be smaller and less homogeneously distributed. In our hands, the use of cobalt 60 irradiation was reflected not just by the easier treatment, but by the decided improvement in the number of patients free of clinically demonstrable disease.

By the time carcinoma has progressed to the point where the clinical classification is Stage III, and to a greater degree when it is Stage IV, the tumors, like all advanced cancers, are so bulky, so firmly entrenched that though their entire volume can be irradiated by what should be an adequate dosage, to expect to obtain eradication or long lasting arrest regularly is unrealistic. Our Stages III and IV statistics in this restricted group are too small to be significant but we feel that we are making modest, gratifying progress. A comparison of survival times in two highly comparable groups, those patients classified in Stages III and IV, whose only treatment consisted of 250 kv. irradiation in one group and cobalt 60 irradiation in the other (Table III), confirms this impression.

SUMMARY

Though a full comparison of late effects is not yet possible, for some time it has been established that patients can tolerate supervoltage irradiation more easily than orthovoltage irradiation. The immediate constitutional and local effects of the former are less severe, and short term palliation of malignant disease can be achieved more successfully and easily.

Data are now beginning to emerge which indicate that the larger doses and more homogeneous distribution permitted by supervoltage irradiation are producing improved survival rates.

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LOWERING THE SKIN TEMPERATURE OF THE IRRADIATED FIELD*

COLD WATER CIRCULATION THROUGH A LUCITE CONE FOR SKIN SPARING WITH CONVENTIONAL ROENTGEN RAYS (300 kv.)

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THE recent renaissance in radiotherapy has resulted from the development and application of various supervoltage machines and radioactive isotopes. The future promises to be an era wherein progress in radiobiology will contribute chiefly to any further advances made in this treatment modality.

In cardiac surgery refrigeration has been employed to help solve some of its problems and subsequently greater progress followed. This paper is concerned with the skin sparing effects which can result when the temperature of the skin field to be irradiated is lowered by refrigeration. It has been noted that additional dosage can be given before the usual radiation tolerance of the skin is reached. This results in an increase in the depth dose. The use of refrigeration with conventional roentgen irradiation has practical economic value, since many radiology departments do not have the availability of a supervoltage machine with its skin sparing effect. There are many departments where one or several conventional machines are idle while a single supervoltage unit is in excessive use. The electron beam, although derived from a supervoltage machine, has little or no skin sparing feature. Thus an impetus to its further use and better management of patients receiving electron beam therapy may also result from this study.

There are other areas of importance; for example, certain drugs may potentiate or give additive effects to the irradiated field. Actinomycin D has been shown to enhance the skin reaction of patients.[2] This could possibly be counteracted if the skin were irradiated at a lower temperature. Future drug developments may make this mode of treatment with refrigeration even more important. A second area would be in retreating patients with this method to lessen the possibility of skin necrosis. Thirdly, the skin overlying soft tissue tumors may be better approached in this manner. Finally, younger patients receiving adequate irradiation are less likely to develop pronounced skin changes during their long follow-up period.

In the literature reports can be found of various systems (*e.g.*, frogs' eggs, *Drosophila* larvae, spores, wheat plantlets, etc.) that have been studied following a combination of lower temperatures and irradiation. However, the reports germane to our study are those of the skin effects at the time of irradiation.[1,3–9] These together with our clinical group of patients are presented in Table 1. One can see that there is no uniformity of opinion among the earlier investigators that lower temperatures of the skin cause an increase in the resistance of the skin to irradiation. The present study gives substantial evidence that the skin at 50–55° F. temperatures is spared from the usual degree of changes that one is accustomed to seeing with adequate radiation doses.

METHOD

The experiment required: (1) developing a special water cone, (2) a means of circulating cooled water through the cone, (3) a method of measuring skin temperatures,

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Table I

OBSERVATIONS ON LOWERED TEMPERATURES OF SKIN AT TIME OF IRRADIATION

Author	Subject	Area	Method	Result
1. Simpson[9] (1916)	4 patients (exophthalmic goiter)	Thyroid region	Ice bag	Increased reaction
2. Martin, and Caldwell[7] (1922)	2 rabbits	Abdomen	Ice bag and box	Seems to accentuate the reaction
3. Mottram[8] (1924)	Rats	Flank and tails	Ice water near 0° C.	In region of 0° C. decided increase in the sensitiveness of the skin. At 6° C. no effect
4. Evans *et al.*[4] (1941)	Rats	Dorsal and ventral surfaces	Packed in crushed ice	Lower temperatures increased resistance of skin
5. Evans and Kerr[5] (1943)	8 patients (carcinoma of cervix)	Anterior, posterior and lateral pelvic portals	Water cooled aluminum tipped cone	57–66° F. Individual variation high, low temperature of doubtful value
6. Barth and Wachsmann[1] (1947)	7 patients	Anterior thigh	Small aluminum water cone	At higher temperatures increased effect. Not very temperature dependent at 32°–68° F.
7. Liebner *et al.* (1961)	31 patients (carcinoma of cervix)	Lower abdomen and buttocks	Large lucite and water cone	Definite skin sparing with skin temperature reduced to 50°–55° F.

and (4) selecting a suitable group of patients.

To cool the skin, a special truncated cone was designed which is shown in Figure 1 applied to the lower anterior abdomen. The cone is made of methyl methacrylate (lucite). Its height is 23.5 cm., which when attached to our unit gives a treatment distance of 50 cm. The attached end measures 12.8 cm. by 12.8 cm. The sides are made of the same plastic 0.7 cm. thick. The free or patient contact end of the cone measures 16 cm. by 20.5 cm. and is made into two separate compartments $8 \times 15 \times 0.5$ cm. with a 4 cm. lead strip separating them. Figure 2 shows the applying surface of the cone rotated into a horizontal position. The cooling compartment is adapted with two 0.5 cm. openings. One is the inlet of the cooled water and the other is the outlet to maintain a constant circulation. Insulated tubing 2 cm. in diameter is used to connect the cone to the water supply. The other compartment is filled with a 0.5 cm. layer of water by using a needle and syringe through one small screw cap opening. This room temperature compartment (control side) maintains its volume indefinitely, requiring water change only when turbidity occurs. The volume of each compartment is 20 cc. Victoreen thimble chamber readings

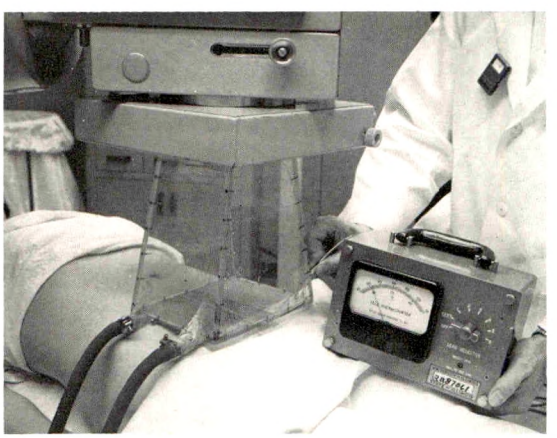


Fig. 1. Special lucite cone devised to circulate cold water over one 8×15 cm. skin field of the lower abdomen. The other side is the control. Also shown is the thermistor unit and probe used to record skin temperatures earlier in the study.

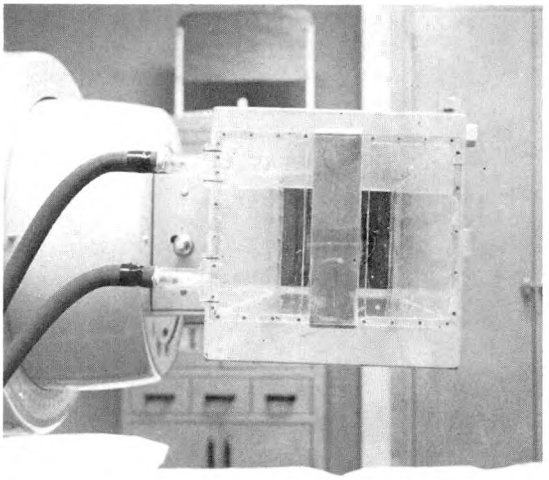


FIG. 2. Water cone rotated into horizontal position. The compartment with the hoses attached provides a 0.5 cm. layer of cooled circulating water. The control, room temperature water, compartment is separated from the other by a 4 cm. lead strip. (Reproduced with permission of *Radiology*.[6])

were made at comparable geometric points under each compartment and found to be the same within the accuracy of the chambers (± 2 per cent). It is interesting to note that this amount of water and lucite causes little absorption (about 3 per cent).

The cooled water was first obtained and circulated by attaching the hose to a nearby cold water faucet in the room as shown in Figure 3. When there was promise of favorable results, a more adequate means of refrigeration was employed to obtain more accurately stabilized lower temperatures. This was accomplished by a cooling unit consisting of a $\frac{1}{2}$ horsepower compressor with a 3 gallon brine solution tank (Fig. 4). A glycol solution was used which consisted of 40 per cent glycol and 60 per cent water. A circulating pump completed the unit.

Preliminary temperature readings of the skin and cone before, during and after therapy were made with a thermistor apparatus (Fig. 1).* The probe is a regular surface "banjo" type for skin temperatures. In order to obtain multiple readings almost simultaneously of the undersurface of both compartments in air and in contact with

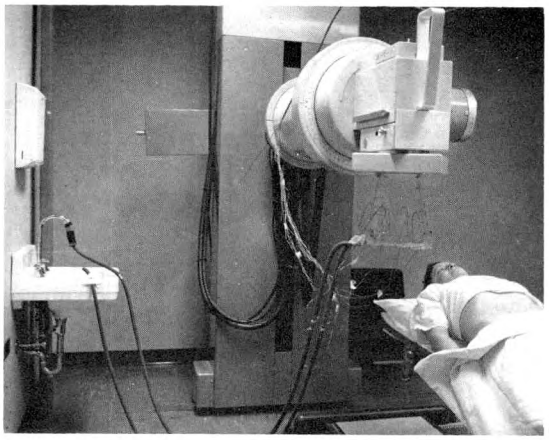


FIG. 3. Water cone attached to a water faucet, which was the original cooling source in the study. Thermocouples are attached to the cone.

the skin, resort was made to thermocouples. The thermocouples are copper, constantan elements. Five thermocouples were attached to the undersurface of each water compartment so they finally would be interposed between the cone and the skin of the patient (Fig. 3 and 4). One thermocouple was placed in the cooling tank source, and a reference thermocouple was placed in a Dewar flask (thermos) containing ice chips and water (Fig. 4 and 5). The thermocouples were attached to an electronic potentiometer† which had a range of volt-

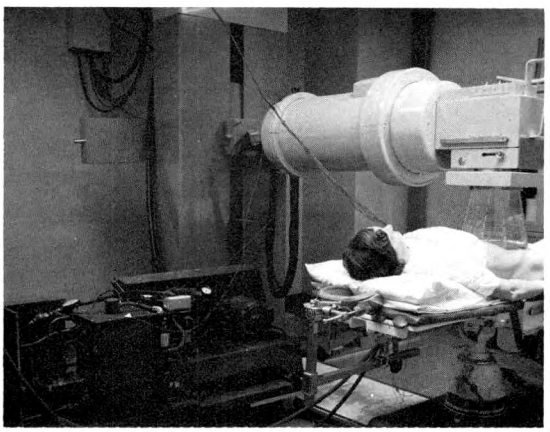


FIG. 4. Cooling unit used to circulate cold water. Unit consists of a $\frac{1}{2}$ horsepower compressor with a 3 gallon brine solution tank. A thermocouple can be seen entering the circulating tank. (Reproduced with permission of *Radiology*.[6])

* Tele-thermometer, Yellow Springs Instrument Co.

† Minneapolis Honeywell-Brown Instrument.

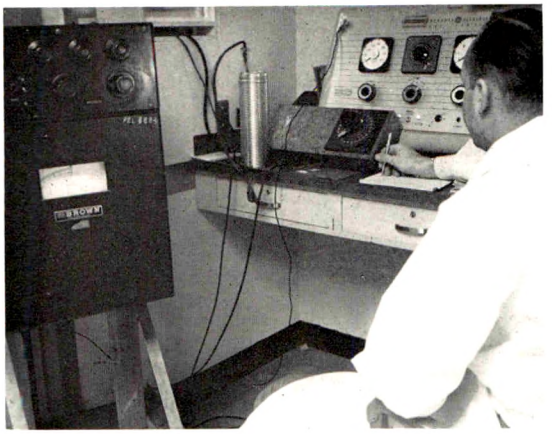


Fig. 5. Electronic potentiometer used with thermocouples, seen in Figures 3 and 4, to obtain skin-cone surface and water source temperatures. A reference thermocouple is shown placed in a Dewar flask containing ice and water.

age up to 70 mv. (Fig. 5). A set of readings was made with the cone in contact with the patient's lower abdomen and also free of any surface (Tables II and III).

Patients with carcinoma of the cervix were selected because of the importance placed on the treatment of this disease. Also, relatively large divided anterior skin fields could be used on the lower abdomen as well as large posterior fields on the pelvis. Thus, a control (noncooled) area of skin

Table II

TEMPERATURE DISTRIBUTION ON CONE SURFACE
(face upward)

Thermocouple No.	Degrees Fahrenheit
2	47, 48, 48
4	43, 45, 46, 45, 44, 44
6	51, 51
7	48, 48
9	51, 51, 52, 51, 55
11	51, 52
10	80, 80, 79, 79, 79
12	80, 79, 79, 83
14	80, 82, 79
15	81, 80, 79, 79

Reference unit 36° F. Cooling unit tank 43–45° F. (Thermocouple No. 4).

Note: Determinations obtained at thermocouple sites (see Fig. 16).

Table III

TEMPERATURE DISTRIBUTION WITH THERMOCOUPLES BETWEEEN CONE AND SKIN OF ABDOMEN

Thermocouple	1 min.	3 min.	7 min.	10 min.
2	74°	64°	61°	60°
6	75	70	68	67
7	69–62	63–55	55–51	53
9	74	68–62	66–62	66–62
11	53	52	52	52
10	86	87	88	87
14	91	93	94	94
15	91	90	90	90

Reference unit 36° F. Cooling unit tank 43–45° F. (Thermocouple No. 4).

Note: Optimal time for cooling the skin prior to irradiation is 2 to 3 minutes.

separated by a 4 cm. strip from a cooled area of skin could readily be had on both the front and back on each patient. A fairly reasonable contact application of the cones could be obtained since the surface contours would not vary as greatly as those of the head and neck areas, for example.

The only single variable in the experiment, is the lowered temperature of the skin of one irradiated field. The same time, quality, and quantity of radiation and the same identical compression and geometry of both sides give adequate control of other possible variables.

In the first stages of the clinical experiment, only white patients were sought so as to better detect and evaluate any early differences in erythema. Some difficulty was encountered since at that time Negro patients were the only ones available. It was therefore decided to treat patients consecutively. When treatment is carried to advanced erythema and desquamation, it is possible to evaluate the cooled side from the control area regardless of race.

The management of these patients did not deviate in any other way from our regular method of treating carcinoma of the cervix. Generally, radium insertion is made first and then external radiation is given. This is interrupted briefly to give the second

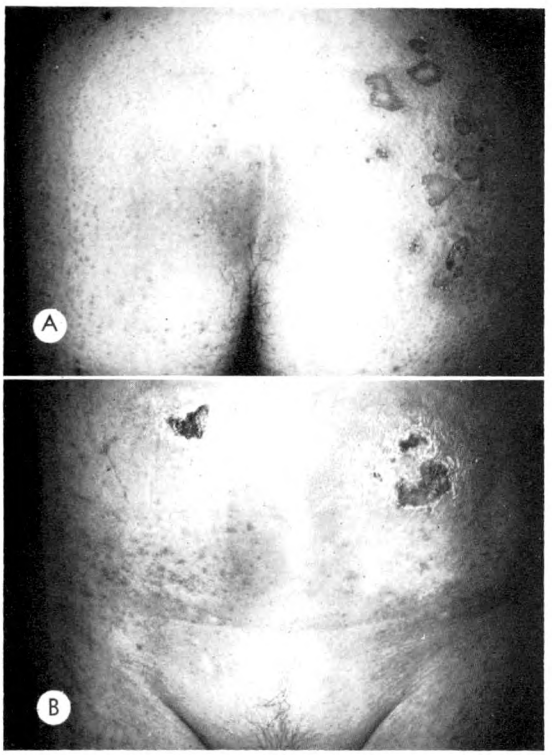


FIG. 6. (*A*) Patient No. 4, white. Posterior portals 6 weeks after receiving 3,000 rads. The left side is the cooled field. (*B*) One month after anterior portals had received 3,900 rads. The cooled right side had poor application of cone in this area.

course of radium about 2 weeks after the first course. The intracavitary radium consists of a separate tandem containing 27–35 mg. and Manchester ovoids having a combined total of 36–48 mg. of radium. These are generally applied in 72 and 50 hour courses. The external radiation we use is 300 kv., half value layer 4 mm. Cu, 19.5 ma. at a 50 cm. treatment distance. Both anterior and posterior fields are treated alternately with a skin dose of 300 rads to each 8 × 15 field.* With the use of the cooled water cone, the right anterior and the left posterior portals became the cooled fields. This system yielded identical depth doses to the parametria. The cone was applied by three different residents who were on the service during the study period. The treatments were given 5 times a week for an average of 5 weeks. The skin reaction was usually carried to moist desquamation.

* For conversion factor (r to rad) *cf.* Murphy, W. Radiation Therapy, p. 4. W. B. Saunders Co., Philadelphia, Pa., 1959. The dosage figures are all reported to the first two significant digits.

RESULTS

During the earlier part of the study, cold water from the faucet was used (Fig. 3). In Table IV are shown the 10 consecutive patients, No. 1 to 10, who received cooling by tap water. These patients were referred for treatment from the late summer to early winter of 1960. Subjectively, all of these patients had less pain and discomfort on the cooled side. Seven of the 10 were considered to have good objective sparing effect, showing less erythema, desquamation, and atrophic changes on follow-up. The remaining 3 had less striking objective changes, but a difference could be detected between the two sides. Figures 6, *A* and *B*; 7; 8; and 9 show the difference between the side cooled by tap water at the time of radiation and the noncooled side.

When these results were obtained from simple cold tap water cooling, we felt encouraged to try a refrigerated cooling source. Thereby fluctuations of tap water temperature with various seasons of the year could be eliminated, and a more controlled study of the temperature relationship of the cone surfaces could be obtained.

In 21 consecutively irradiated patients, the refrigeration unit was used. These are listed as patients No. 11 to 31 in Table IV.



FIG. 7. Patient No. 6, Negro. Anterior portals 6 weeks after receiving 4,200 rads. The right side is the cooled side; severe moist desquamation of the opposite side is present. Gentian violet was applied bilaterally to the skin fields.

Among these 21 patients, there were 9 Negroes, 1 of whom had scleroderma (No. 31), and 3 (No. 27, 29 and 30) who received actinomycin D therapy during the course of radiation. From the total group, 11 patients showed good skin sparing, while 7 had mild objective evidence of benefit. Only 2 patients did not seem to show any significant sparing effect; both were Negroes. One patient (No. 25) was lost to follow-up study. Figures 10; 11, *A*, *B* and *C;* and 12 show some of the changes observed.

Several of the patients who showed the skin sparing effect were given additional dosage to the cooled anterior and posterior fields. These were patients No. 15, 16, 17, 18 and 21, shown in Table IV with the exact dosages given. It was possible to administer with ease an additional 1,400 rads to the cooled skin. We felt that more could have been given but had some trepidation in delivering higher doses since we did not know what the end results would be. Figure 13 shows patient No. 16, 6 months after treatment, whose cooled right lower abdominal field received 1,200 rads more than the left noncooled side.

DISCUSSION

In order to correlate these clinical findings with temperature, thermocouple readings were made. Figure 16 shows the cone surface and the number and site of the thermocouples. Figure 14 illustrates diagrammatically the thermocouple readings in two significant studies. One is concerned with the temperature distribution on the cone surface in air. The values are presented in Table II. The mean temperature of our refrigerated water was 44° F. as shown by thermocouple No. 4. The mean temperature of the cooled surface was 51° F., while that of the other side was 80° F. The second study shows the temperature distribution with the thermocouples between the cone and the skin of the abdomen. The various time intervals from 1 to 10 minutes are listed in Table III. After contact with the

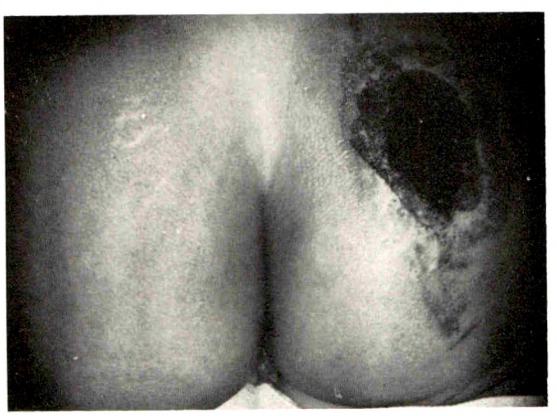


FIG. 8. Patient No. 8, white. One month after receiving 3,900 rads to posterior portals. Gentian violet was applied on the large denuded area of the noncooled field. Note only minimal change in cooled field where poorest contact was made.



FIG. 9. Patient No. 9, white. Posterior portals 1 month after beginning treatment and after receiving 3,900 rads, with gentian violet applications. The cooled side is on the left.



FIG. 10. Patient No. 22, white. Anterior portals after receiving 4,900 rads in 6 weeks. The patient's right side with the pencil taped laterally is the cooled field.

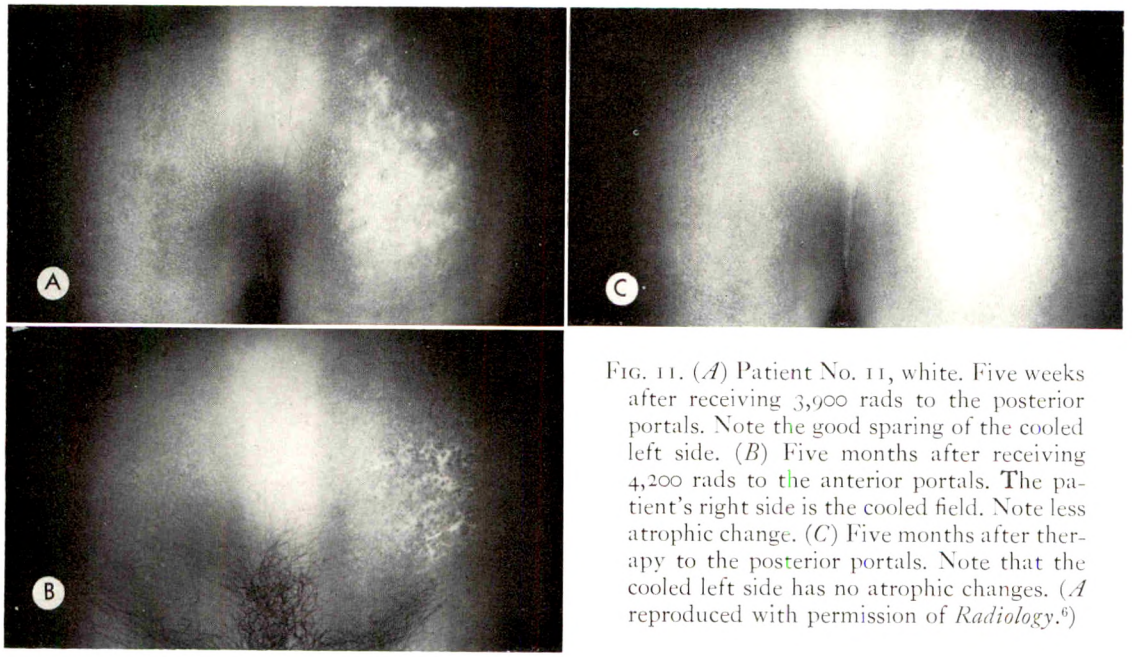


FIG. 11. (*A*) Patient No. 11, white. Five weeks after receiving 3,900 rads to the posterior portals. Note the good sparing of the cooled left side. (*B*) Five months after receiving 4,200 rads to the anterior portals. The patient's right side is the cooled field. Note less atrophic change. (*C*) Five months after therapy to the posterior portals. Note that the cooled left side has no atrophic changes. (*A* reproduced with permission of *Radiology*.[6])

patient's abdomen for 10 minutes, the mean temperature of the cooled surface rose to 64° F., while that of the uncooled side rose to 92° F. A further study of Table III shows that one need only to cool the skin for 2 minutes under this system prior to giving the radiation treatment. Our average external irradiation treatment time is 5 to 6 minutes. Therefore, the total set-up and treatment time falls well within a range of low stabilized readings. There should be no delays in the department when treating patients in this manner.

Figure 15 shows several studies made with the thermistor unit of patients in whom tap water cooling of the skin was employed. The tap water temperature at that time was 56° F. The average reduction in skin temperature was 24° F. in 5 minutes. Skin temperatures at the conclusion of treatments were 73° F. Figure 16 shows studies using the refrigeration unit and one can see the greater uniformity. The average reduction in skin temperature was 41° F. in 2 minutes. The skin temperature at the conclu-



FIG. 12. Patient No. 27, white. Posterior portals after receiving 2,700 rads only $3\frac{1}{2}$ weeks after beginning of treatment. Patient received actinomycin D which enhances the skin effect of the non-cooled field of the right side.

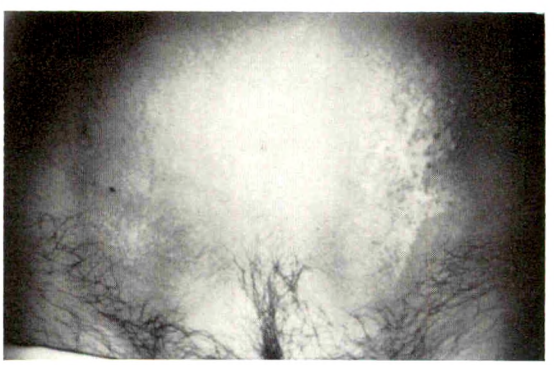


FIG. 13. Patient No. 16, white. Anterior skin fields 6 months after treatment. The patient's right side received 4,900 rads with cooling and the left side 3,700 rads without cooling. Note the sparing effect produced by cooling even with an additional 1,200 rads. (Reproduced with permission of *Radiology*.[6])

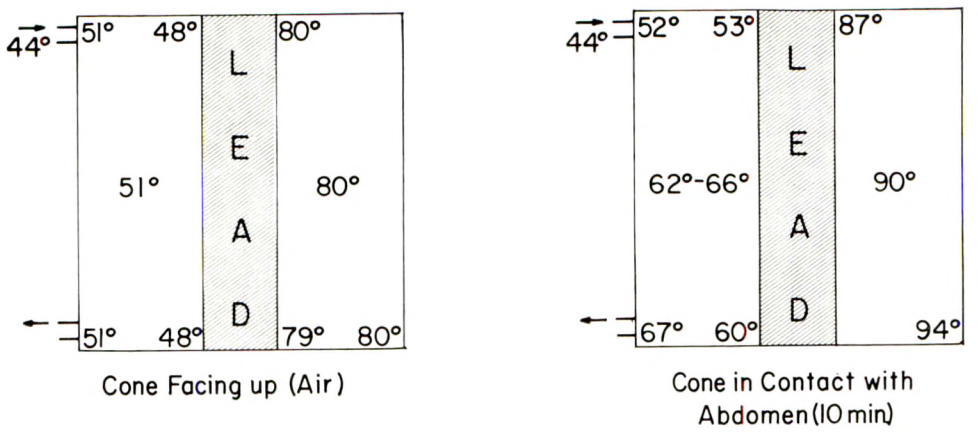


Fig. 14. Temperature readings at the thermocouple sites shown in Figure 16, under two conditions.

sion of treatments had a mean of 53° F.

Patients tolerated these temperatures without discomfort. In thin patients the rigidity of the cone surface was at times disadvantageous. The bony prominences of the ilium in the scaphoid type of abdomen prevented good contact with the anterior lower abdomen for adequate cooling of the skin. As a rule, the posterior portals over the upper buttock areas made better contact, and at times this region showed the more striking sparing effects. At present, we are interested in a cooling air source so as to be able to treat irregular contours, as well as patients with head and neck lesions. When one considers that the results were obtained at skin temperatures of 50–55° F. and only routine care in applying the cone was given by different persons, certainly

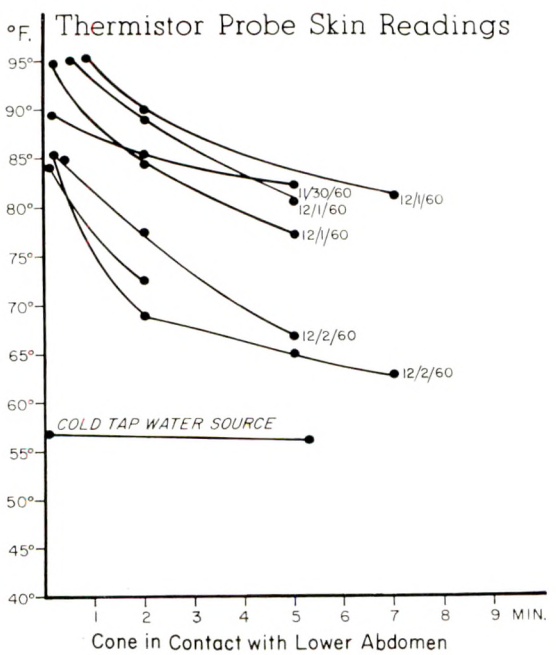


Fig. 15. Variety of response produced by the tap water source with thermistor probe study.

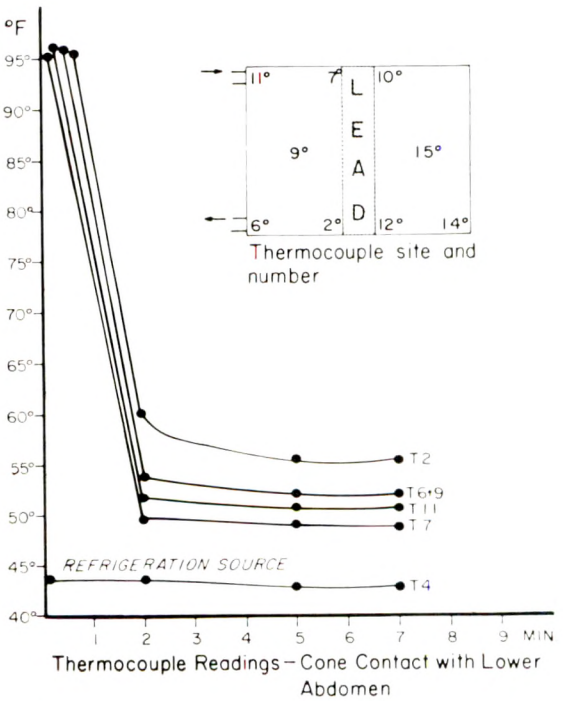


Fig. 16. Thermocouple site and number with temperature response (see Table IV).

TABLE IV

SUMMARY OF CASES

Patient	Age	Race	Date of First Treatment	Extent of Disease (Stage)	Dosage to Skin Fields	Remarks
1. O. K.	69	W	8–9–60	2	Anterior, right and left 4,200 rads Posterior, right and left 4,200 rads	Good sparing effect in pendulous abdomen. Cool tap water
2. V. C.	55	W	8–9–60	2	Anterior, right and left 4,500 rads Posterior, right and left 4,500 rads	Good sparing effect. Cool tap water
3. A.S.	45	W	9–1–60	3	Anterior, right and left 3,900 rads Posterior, right and left 3,900 rads	Only mild sparing. Tap water cooling
4. M.Z.	62	W	9–1–60	1	Anterior, right and left 3,900 rads Posterior, right and left 3,900 rads	Good sparing effect. Cool tap water
5. J.S.	49	W	9–12–60	2	Anterior, right and left 3,900 rads Posterior, right and left 3,600 rads	Good sparing, anteriorly and posteriorly. Cool tap water
6. B.B.	63	N	10–7–60	3	Anterior, right and left 4,200 rads Posterior, right and left 3,900 rads	Good sparing effect evident by less fibrosis and atrophy. Cool tap water
7. A.F.	38	W	10–13–60	3	Anterior, right and left 3,900 rads Posterior, right and left 4,200 rads	More sparing seen posteriorly. Cool tap water
8. M.P.	49	W	10–21–60	3	Anterior, right and left 3,900 rads Posterior, right and left 3,900 rads	Good sparing, especially posteriorly. Cool tap water. Expired 7/61.
9. Y.G.	58	W	10–21–60	3	Anterior, right and left 3,900 rads Posterior, right and left 3,900 rads	Good sparing, especially posteriorly. Cool tap water.
10. A.R.	81	W	11–7–60	1	Anterior, right and left 3,300 rads Posterior, right and left 3,300 rads	Mild sparing seen early. Cool tap water

TABLE IV—*Continued*

Patient	Age	Race	Date of First Treatment	Extent of Disease (Stage)	Dosage to Skin Fields	Remarks
11. A.M.	45	W	11–17–60	2	Anterior, right and left 4,200 rads Posterior, right and left 3,900 rads	Good sparing early and late. Cool tap water and refrigeration
12. E.R.	39	N	11–25–60	3	Anterior, right and left 3,900 rads Posterior, right and left 4,200 rads	No decided change detected
13. L.H.	34	N	12–1–60	3	Anterior, right and left 3,600 rads Posterior, right and left 3,600 rads	Whole pelvis technique of questionable benefit
14. M.G.	64	W	12–12–60	3	Anterior, right and left 4,100 rads Posterior, right and left 4,100 rads	Mild benefit seen in healing and late stages from cooling
15. V.T.	30	W	12–12–60	3	Anterior, right 5,700 rads Anterior, left 4,300 rads Posterior, right 3,500 rads Posterior, left 4,900 rads	Cooled areas spared. Increased dose. Refrigeration
16. L.P.	46	N	12–16–60	3	Anterior, right 4,900 rads Anterior, left 3,700 rads Posterior, right 3,400 rads Posterior, left 4,600 rads	Good benefit. Increased dose on cooled side. Refrigeration
17. A. McK.	32	N	12–20–60	2	Anterior, right 4,200 rads Anterior, left 3,600 rads Posterior, right 3,300 rads Posterior, left 3,300 rads	Only minimal benefit noted
18. E.B.	79	W	12–22–60	3	Anterior, right 4,600 rads Anterior, left 3,300 rads Posterior, right 3,300 rads Posterior, left 4,600 rads	Cooled side received 1,300 rads more with less change
19. H.A.	39	W	12–22–60	1	Anterior, right and left 4,000 rads Posterior, right and left 4,000 rads	Slight benefit on cooled sides
20. E.B.	54	W	1–5–61	3	Anterior, right and left 4,200 rads Posterior, right and left 4,200 rads	Good effects with refrigeration

TABLE IV—*Continued*

Patient	Age	Race	Date of First Treatment	Extent of Disease (Stage)	Dosage to Skin Fields	Remarks
21. J.C.	42	W	1–12–61	3	Anterior, right 5,300 rads Anterior, left 3,900 rads Posterior, right 3,900 rads Posterior, left 5,300 rads	Increased dose of 1,600 rads more given on protected cooled sides
22. L.W.	50	W	1–12–61	2	Anterior, right and left 4,900 rads Posterior, right and left 4,600 rads	Good benefit seen especially anteriorly
23. S.K.	33	W	1–12–61	3	Anterior, right and left 4,500 rads Posterior, right and left 4,500 rads	Mild benefit anteriorly
24. E. McW.	71	N	1–18–61	3	Anterior, right and left 3,500 rads Posterior, right and left 3,500 rads	Mild benefit posteriorly, especially evident by less atrophy
25. I.C.	71	W	1–27–61	2	Anterior, right and left 2,300 rads Posterior, right and left 2,100 rads	Lost to follow-up
26. A.R.	62	N	2–3–61	3	Anterior, right and left 3,800 rads Posterior, right and left 3,500 rads	Less fibrosis in cooled areas
27. S.P.	45	W	3–21–61	3	Anterior, right and left 3,600 rads Posterior, right and left 4,200 rads	Had actinomycin D therapy. Sparing posteriorly
28. D.J.	45	N	4–18–61	1	Anterior, right and left 4,500 rads Posterior, right and left 4,300 rads	Mild benefit from cooling posteriorly
29. A.K.	46	W	5–4–61	3	Anterior, right and left 3,400 rads Posterior, right and left 3,700 rads	Had actinomycin D therapy. More sparing effect posteriorly
30. W.H.	26	W	5–11–61	3	Anterior, right and left 4,200 rads Posterior, right and left 4,200 rads	Had actinomycin D therapy. More sparing effect posteriorly
31. E.B.	53	N	5–24–61	3	Anterior, right and left 3,800 rads Posterior, right and left 4,200 rads	Had scleroderma. Mild sparing

more strikingly consistent results should be obtained at a slightly lower temperature with better applicability of the cooling source to the area of skin. Also to more adequately spare the skin, it may be necessary to cool an area perhaps one and one-half to two times the size of the actual irradiation field in order to gain maximum advantage.

Our experiment indicated that the increased skin changes resulting from combining actinomycin D and radiation therapy could be lessened by cooling. This was demonstrated especially in patient No. 27 (Fig. 12).

Additional dosage was given to the areas which showed the sparing effects in 5 patients. The amount that can be given will vary from patient to patient, depending upon the effectiveness of cooling and the tolerance of the patient. Certainly, 1,200 r can be given to the routine case and probably 2,000 r can be given occasionally with still some evidence of sparing being manifested (Fig. 13). These preliminary observations seem to be in agreement with the experiments of Evans *et al.*[4] on rats. They found in the newborn rat that skin with lowered temperature required 1,200–1,700 r more before an injury was produced than skin exposed at room temperature.

With the use of large irradiation fields (*e.g.*, pelvis), the conventional depth dose value at 10 cm. is 38 per cent. With an additional 1,200–2,000 r to skin that has been cooled, the depth dose percentage is increased to 50–53 per cent. This value equals the depth dose at 10 cm. for cobalt irradiation.

SUMMARY AND CONCLUSIONS

1. In 31 cases of carcinoma of the cervix, temperatures were lowered to 50–55° F. in the treatment area of the lower right abdomen and the left buttock during irradiation.

2. The cooling was performed by means of circulating water through a lucite cone. Initially, cold tap water was used and, more recently, a refrigeration unit.

3. Temperature distribution studies of the cone surface in air and in contact with the patient's skin were made. Various time intervals were studied to indicate the optimal time of irradiation.

4. Nearly all of the patients' subjective complaints were referable to the uncooled treatment side. Eighteen patients showed good objective sparing effect, *i.e.*, less erythema, desquamation and atrophic changes on the cooled side.

5. Preliminary observations suggest that 1,200 to 2,000 r could be given additionally to the cooled skin fields, increasing the depth dose at 10 cm. from the usual 38 per cent to 50 per cent. The latter equals the depth dose of cobalt 60 teletherapy at 10 cm.

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THE AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE

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EDITORIAL

THE QUESTION OF CHEMICAL POTENTIATORS IN RADIATION THERAPY*

THE discovery of any potentiator in radiation therapy which will increase the differential between normal and cancer cells and render the cancer cells more susceptible to radiation would be of immeasurable value in the over-all treatment of cancer.

Aisenberg[1] has commented that "Despite great progress in understanding the energy metabolism of tumors and an equal progress in defining the biochemistry of tumors in general and the carcinogenic activity of chemical, physical, and viral agents, the fundametal nature of the neoplastic process remains unknown." He also thinks that the biochemical approach to tumor metabolism represents the most promising one to the understanding of the neoplastic process.

Del Regato,[9] who believes in the investigation of any agents capable of specifically potentiating the biologic effects of radiation, has pointed out some of the difficulties involved in such a study. The techniques of radiation therapy are usually much more varied than are surgical procedures. Some outstanding institutions may not have equally outstanding radiotherapists and adequate equipment and trained personnel. Radiotherapeutic experiments often cannot be analyzed on a short term basis. The randomization of patients may prevent some patients from receiving radiation therapy which might be curative since radiation therapy can be curative.

There are many investigators who doubt that there is any potentiating effect when chemotherapy is combined with radiation therapy. For example Karnofsky[13] stated "X-rays are given in combination with chemotherapeutic agents for various reasons, but the clinical data suggesting that certain chemicals can potentiate the tumoricidal effects of local irradiation are not convincing." Of the numerous attempts which have been made to find possible potentiators, one of the most promising has been the use of increased oxygen concentration during radiation therapy. This method is still undergoing clinical investigation.[5–7,12]

During the past two decades the specialty of radiation therapy has become more advanced, has received better recognition, and its importance has been more fully appreciated. Factors which have brought about this change have been the better training of the radiotherapist, more tendency to specialize only in radiation therapy, better equipment, and improved methods of dosimetry. With the beginning of the chemotherapy program and particularly during the past 2 years has come the realization that if chemotherapeutic compounds can be found which will potentiate the effects of ionizing radiation then considerable additional progress will be made.

Dunphy,[10] in 1958, stated that "The hazards of local implantation, the great importance of experience in the recognition and interpretation of gross pathology during the operative procedure, the need for supplementary irradiation or hormonal therapy in certain instances, and the adoption of special measures, such as local chemotherapy or pre-operative irradiation to prevent dissemination are aspects of

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cancer surgery which require that it be performed by the most experienced and specially trained surgeons."

Similarly, it may be stated that the radiotherapist—the radiologist who treats malignant lesions—must know the life history of the disease, the indications and contraindications for surgery, must be able to promptly recognize complications which may occur during radiation therapy, must be able to manage ascites, pleural effusion, or infections, understand the value of hormone and chemotherapy, and be responsible for the over-all management of the patient while under his immediate care. He must accept calculated risks in the successful treatment of this disease.

Although some individuals may have misgivings about the role of chemotherapy in the treatment of cancer, it has acquired an important place in the management of this disease. Chemotherapy appears to offer the only possible hope for curing or controlling the disease when it is widespread. Known curative methods such as surgery and/or radiation therapy which have been highly effective in a number of types of localized cancer are ineffective in the control of disseminated disease. Although approximately one third of the cancer patients are being cured by curent methods, the majority of the patients cannot be helped until new methods or new drugs have been discovered.

Chemotherapy is experimental at the present time. The frequency with which cancer cells are found in the blood and in the operative sites plus the failure of known treatment methods is the basis for its use. However, a proper amount of caution must always be exercised and proven methods should not be discarded. A sense of balance between enthusiasm and conservatism must be maintained.

It is timely that a word of warning be given—the injudicious use of chemotherapy will not only do harm but may actually set back the program. Chemotherapeutic agents are highly toxic and unless given in adequate doses with proper safeguards no appreciable results will be obtained. The morbidity is high and also an increased percentage of mortality will occur. Chemotherapeutic agents such as 5 fluorouracil cannot be administered casually or occasionally. A definite program must be formulated and treatment must be administered by adequately trained personnel.

It is hoped that, as a result of the all-out effort sponsored by the Cancer Chemotherapy National Service Center which was established in 1955, a major breakthrough will eventually result in attempts to control cancer. It is doubtful if a single drug will ever be developed which will uniformly affect all types of cancer; different drugs will probably be needed for the different types of cancer.

There must be more rigid criteria for determing clinical improvement. At the present time a period of 2 months is used by many investigators. There should be (1) measurable decrease in the size of the lesion, (2) subjective improvement, (3) leveling off or reversal in the downward weight curve, and (4) improvement in performance status; all for a period of at least 4 months and preferably 6 months after treatment. The early reported results of radioactive isotope therapy in the control of pleural effusions and of ascites and of the results of hormone therapy in breast cancer certainly were based in part on emotion and enthusiasm. Closer observation and a longer period of control soon enabled one to assess the true value of these methods of therapy.

Too much haste in the chemotherapy program is conducive to too much waste. The concentration on the fullest use of the present compounds alone or in combined therapy by institutions which have the experienced personnel available for the maintenance of excellent records and adequate material should certainly prove most valuable. Many of the older chemical compounds are just as effective as the newer ones; however, there appears to be a tendency to pick up each new compound as soon as it is developed and quickly test it on a variety of cases, then rush inadequate data

into print. Specific criteria with a long enough survival time in order to evaluate the effect of the drugs are essential.

Some of the prerequisites for a good chemotherapy program are: (1) adequately trained medical staff; (2) sufficient personnel for keeping good records; (3) research beds; (4) laboratory facilities for the program; and (5) a good follow-up system.

The results of Reese *et al.*,[15] and duV. Tapley[17] in the treatment of retinoblastoma by combined radiation therapy and triethylene melamine (TEM) have often been referred to as an example of the potentiating effect of the chemical agent. Kligerman,[14] who has closely observed this study, states that "One cannot say as yet that TEM has contributed to the salutory effect in those children so treated."

D'Angio *et al.*,[8] Farber,[11] and Tan *et al.*[16] are of the opinion that actinomycin D potentiates the effects of radiation therapy in the treatment of Wilms' tumors. They believe that there is a reduction in the time required for the normal progression of radiation effects, that an early erythema is produced in the area which is irradiated and that the enhanced skin manifestations are more severe the higher the combined dosages. It can be stated with certainty that the normal skin effect was enhanced but does this hold true for the tumor? Many physicians have had the experience of having patients with malignant tumors live a long time following a low total irradiation tumor dose. Since the patients with Wilms' tumor can live for long periods of time, it is difficult to assess the amount of potentiation unless the patients are in a randomized study. Altman[3] also believes that there is a potentiation of effect when actinomycin D and roentgen therapy are used concomitantly. The survival of individual cells after treatment with chemotherapy and irradiation as determined by tissue culture techniques does not necessarily mean that any potentiating effect so noted will be applicable to animals or to humans.

Vermund *et al.*[18] reported a study of sarcoma 180 transplanted to Swiss Webster albino mice and mammary adenocarcinoma originating spontaneously in inbred Z (C_3H) mice and transplanted for two generations in the same strain. Treatments with 5 fluorouracil, actinomycin D or cytoxan and fractionated roentgen therapy resulted in increased inhibition of the growth of the tumors as well as prolonged survival of the animals when compared to either treatment method used alone.

Alexander *et al.*[2] made a comparative study of the palliative effects of radiation therapy, radiation therapy plus nitrogen mustard, and radiation therapy plus amethopterin and actinomycin D in combination, in the treatment of bronchogenic carcinoma. There were 112 patients with advanced bronchogenic carcinoma in the three groups. The best objective and subjective responses were obtained in the group treated with radiation therapy, amethopterin and actinomycin D, but the survival period was by far the shortest of all.

There are individual reports of the successful palliative and possible curative therapy of patients with cancer treated by chemotherapy but one does not find reports of dramatic complications terminating in sudden death in which the host immune reactions have been overwhelmed. We are all aware of the existence of such cases.

Bagshaw[4] has suggested that a clinical study be made using patients with the type of neoplastic disease in which there has been considerable radiotherapeutic experience. The neoplasm should not be one in which a high cure rate by irradiation alone is anticipated nor one in which the expected cure rate is very low. He believes that patients with carcinoma of the cervix, Stage III, or with carcinoma of the bladder would fall into this category. The patients could be randomly separated into two groups: one group treated by radiation therapy alone and the other group by combined chemotherapy and radiation therapy. The establishment of long term survival rates would be desirable to assay the end result. Such a study without question would be of great value.

Certainly, one important factor that has emerged from the chemotherapy program is a better understanding of the cancer problem. There has developed better cooperation between surgeons, radiotherapists, and others interested in the cancer problem. The necessity for teamwork in the effort to control cancer is more fully realized.

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BOOK REVIEW

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

ACQUIRED SURGICAL LESIONS OF THE ESOPHAGUS. By Clifford F. Storey, M.D., Private Practice, Thoracic and Cardiovascular Surgery, College of Medicine, State University of New York at New York; Formerly, Chief of the Surgical Service and Head of the Department of Thoracic Surgery, U. S. Naval Hospital, St. Albans, New York; Portsmouth, Virginia, and Others. Cloth. Price, $19.00. Pp. 365, with 181 illustrations. Charles C Thomas, 301–327 East Lawrence Avenue, Springfield, Ill., 1962.

In this excellent monograph the author presents his subject from the etiologic, symptomatic and curative standpoint in a concise and easily readable fashion. It is most helpful to have a description of the lesion as well as of the most valuable methods which can be employed in definitive diagnosis coupled with advice as to the techniques for the ameliorating surgery.

A special section is devoted to the problem of hiatus hernia with well illustrated graphic reproductions of the technique for repair. This will prove particularly interesting even if one may not wish to subscribe to the author's belief that, unless there is definite contraindication to surgery, it should be undertaken as soon as a hernia is diagnosed.

The use of esophagoscopy in all lesions of the esophagus is of great value, enabling one to visualize the area in question, permitting biopsy where necessary, and facilitating the removal of foreign bodies when extraction is feasible. The main contraindication to the use of the esophagoscope is instrumental perforation of the esophagus where the danger of enlarging the defect is very great.

Roentgenologic examination of the esophagus utilizing contrast oil techniques and/or barium with fluoroscopy is invaluable in the diagnosis of esophageal pathology and provides a wealth of information of great practical significance.

There are chapters devoted to achalasia, diverticula, reflux esophagitis, ulcer and stricture with much of the author's personal experience added. Both benign and malignant lesions are considered.

The chapter on carcinoma of the esophagus is authoritatively written by Drs. Laforet, Strieder and Lynch. It is based on an analysis of 643 cases with the following results obtained: 42 per cent resectability rate; 39 per cent resection mortality; and a 5 year survival rate of 8 per cent of 97 patients surviving the resection. For supra-aortic anastomosis, the long term survival was 3 per cent and for the infra-aortic anastomosis 10 per cent.

As Dr. Alton Ochsner has so ably stated in the foreword, "This extremely practical, readable, and comprehensive volume should be in the library of everyone interested in esophageal disturbances whether he is a general practitioner, internist or surgeon."

GEORGE A. KLING, M.D.

BOOKS RECEIVED

CANCER; DIAGNOSIS, TREATMENT, and PROGNOSIS. Third edition. By Lauren V. Ackerman, M.D., Professor of Surgical Pathology and Pathology, Washington University School of Medicine, St. Louis, Missouri; and Juan A. del Regato, M.D., Director, Penrose Cancer Hospital, Colorado Springs, Colorado. Cloth. Price, $29.50. Pp. 1,296, with 779 illustrations, 4 in color. C. V. Mosby Company, 3207 Washington Boulevard, St. Louis 3, Mo., 1962.

SURGERY OF THE CHEST. Edited by John H. Gibbon, Jr., M.D., Chairman of the Department of Surgery, Jefferson Medical College, Philadelphia, Pa. Cloth. Price, $27.00. Pp. 902, with many illustrations. W. B. Saunders Company, West Washington Square, Philadelphia 5, Pa., 1962.

TREATMENT OF CANCER AND ALLIED DISEASES. Second edition. VOL. VII. TUMORS OF THE MALE GENITALIA AND THE URINARY SYSTEM. Edited by George T. Pack, M.D., F.A.C.S., and Irving M. Ariel, M.D., F.A.C.S. Cloth. Price, $18.00. Pp. 397, with 436 illustrations. Hoeber Medical Division, 49 East 33rd Street, New York 16, N. Y., 1962.

RADIOISOTOPES IN CARDIOVASCULAR DISEASE. Edited by Charles K. Friedberg, M.D., Cardiologist and Attending Physician for Cardiology, The Mount Sinai Hospital, New York, New York; and (Guest Editor) Solomon Silver, M.D., Attending Physician and Chief, Thyroid Clinic, Mt. Sinai

Hospital, New York, New York. Cloth. Price, $6.75. Pp. 158, with many tables and figures. Grune & Stratton, 381 Park Avenue South, New York 16, N. Y., 1962.

CURVATURES OF THE SPINE. By Emil D. W. Hauser, M.S., M.D., Associate Professor of Orthopedic Surgery, Northwestern University Medical School; Attending Orthopedic Surgeon, Passavant Memorial Hospital, Chicago, Illinois. Cloth. Price, $9.75. Pp. 190, with 123 illustrations. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1962.

PSEUDOARTHROSIS OF THE LONG BONES. By Otto Verbeek, M.D., Orthopaedic Surgeon, Lecturer in Orthopaedics, Municipal University, Amsterdam, The Netherlands; and C. P. Dubbelman, M.D., Rehabilitation Officer. Cloth. Price, $15.00. Numerous pages and illustrations. Year Book Medical Publishers, 35 East Wacker Drive, Chicago 1, Ill., 1962.

IRRADIATION OF MICE AND MEN. By John F. Loutit, D.M., Director, Radiobiological Research Unit, Harwell, England. Cloth. Price, $5.00. Pp. 154, with figures. University of Chicago Press, 5750 Ellis Avenue, Chicago 37, Ill., 1962.

ACTA RADIOLOGICA—SUPPLEMENTUM 213. LEFT HEART AND AORTIC BLOOD FLOW IN THE DOG. By Nils-Magnus Ohlsson. Paper. Pp. 80, with illustrations. Acta Radiologica, Box 2052, Stockholm 2, Sweden, 1962.

DIE KOLPOSKOIE IN DER PRAXIS; EINFÜHRUNG IN DIE FRÜHDIAGNOSTIK DES COLLUMCARCINOMS. By Prof. Dr. Herbert Cramer, Chefarzt der Frauenklinik im Hospital zum Heiligen Geist, Frankfurt, Germany. Cloth. Pp. 117, with numerous illustrations, many in color. Georg Thieme Verlag, Herdweg 63, Stuttgart N, Germany, 1962. In the USA and Canada: Intercontinental Medical Book Corporation, New York 16, N. Y.

DIE ANGIOGRAPHIE DER EINSEITIGEN FUNKTIONSLOSEN NIERE; KLINIK UND EXPERIMENT. By Gerhard Hartmann, Dozent Dr. med. habil., Oberarzt der Chir. Univ.-Klinik Jena; Mit einem Geleitwort von Prof. Dr. med. Heinrich Kuntzen, Jena. Cloth. Pp. 148, with 34 illustrations. VEB Gustav Fischer Verlag, Jena, Villengang 2, Germany, 1962.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Shoreham Hotel, Washington, D. C., Oct. 2–5, 1962.

AMERICAN RADIUM SOCIETY
Secretary, Dr. Justin J. Stein U.C.L.A. Medical Center, Los Angeles 24, Calif. Annual meeting: Mark Hopkins Hotel, San Francisco, Calif., April 1–4, 1963.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary, Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb.
Treasurer, Dwight Vincent Needham, 713 E. Genessee St., Syracuse, N. Y. Annual meeting: Palmer House, Chicago, Nov. 25–30, 1962.

AMERICAN COLLEGE OF RADIOLOGY
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting: Drake Hotel, Chicago, Ill., Feb. 6–9, 1963.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eighth Ave., Spokane 4, Wash. Annual meeting: Atlantic City, N. J., June 16–20, 1963.

AMERICAN BOARD OF RADIOLOGY
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn. The Fall 1962 examination will be held at the Pioneer Hotel, Tucson, Arizona, the first week in December; the deadline for filing applications was July 1, 1962. Please note that at this session Nuclear Medicine will become a mandatory part of the examination. All candidates, excluding re-examinees, who are applying for examination in Radiology or Therapeutic Radiology for the December, 1962 session or thereafter *must submit a Nuclear Medicine application* in addition to their basic application. This applies even to those applicants whose basic applications are on file but who will not yet have appeared for examination. The Spring 1963 examination will be held at the Sheraton Hotel, Philadelphia, Pennsylvania, June 3–7, inclusive. Deadline for filing applications is December 31, 1962. There will be a Special Examination in Nuclear Medicine for diplomates in Radiology or Therapeutic Radiology if sufficient applications are received. The Fall 1963 examination will be held at the Terrace Hilton Hotel, Cincinnati, Ohio, December 2–6, inclusive. Deadline for filing applications is June 30, 1963.

AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE
Secretary-Treasurer, Charles S. Simons, University of Michigan Hospital, Ann Arbor, Mich. Annual meeting to be announced.

ELEVENTH INTERNATIONAL CONGRESS OF RADIOLOGY
Secretary-General, Dr. Carleton B. Peirce, Royal Victoria Hospital, Montreal 2, Quebec, Canada. Meeting to be announced.

EIGHTH INTER-AMERICAN CONGRESS OF RADIOLOGY
Counselor for the United States, Dr. J. A. del Regato, Penrose Cancer Hospital, 2200 North Cascade Avenue, Colorado Springs, Colo. Meeting to be announced.

ALABAMA RADIOLOGICAL SOCIETY
Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place Alabama State Medical Association.

AMERICAN NUCLEAR SOCIETY
Treasurer, Raymond Maxson, 86 E. Randolph St., Chicago, Ill.

ARIZONA RADIOLOGICAL SOCIETY
Secretary, Dr. E. Lawrence Ganter, 1820 E. Polk St., Phoenix 34, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS
Secretary, Dr. John A. Campbell, Indiana University Medical Center, Indianapolis, Ind. Annual meeting: Yale University Medical Center, New Haven, Conn., May 24–25, 1963.

ATLANTA RADIOLOGICAL SOCIETY
Secretary, Dr. Wilson T. Edenfield, 35 Linden Ave., N.E., Atlanta 8, Ga. Meets monthly, except during three summer months, on second Friday evening.

BLOCKLEY RADIOLOGICAL SOCIETY
Secretary, Dr. Bernard J. Ostrum, 2412 North 52nd St., Philadelphia, Pa.

BROOKLYN RADIOLOGICAL SOCIETY
Secretary, Dr. Leslie L. Alexander, 257 New York Ave., Brooklyn 16, N. Y. Meets first Thursday of each month October through May.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. Edward A. Dunlap, Jr., 35 Danbury Lane, Kenmore 17, N. Y. Meets second Monday evening each month, October to May inclusive.

CALIFORNIA RADIOLOGICAL SOCIETY
Secretary, Dr. L. Henry Garland, Suite 1739, 450 Sutter St., San Francisco, Cal. Meets annually during meeting of California Medical Association.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY
Secretary, Dr. Edward W. Carsky, Crouse-Irving Hospital, 820 S. Crouse Ave., Syracuse, N. Y. Meets first Monday each month October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY
Secretary, Dr. Dana R. Schmidt, 1500 West Third Ave., Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

CENTRAL SOCIETY OF NUCLEAR MEDICINE
Secretary, Dr. Robert S. Landauer, Radiation Center Bldg., 1903 West Harrison St., Chicago 12, Ill.

CHICAGO ROENTGEN SOCIETY
Secretary, Dr. Abram Cannon, Chicago Wesley Memorial Hospital, 250 E. Superior St., Chicago 11, Ill. Meets second Thursday of each month, October to April except December at the Pick-Congress Hotel at 8:00 P.M.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary, Dr. Ward D. Heinrich, Huron Road Hospital, Cleveland 12, Ohio. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.

COLORADO RADIOLOGICAL SOCIETY
Secretary, Dr. Seward Imes, 1845 High St., Denver, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

CONNECTICUT VALLEY RADIOLOGIC SOCIETY
Secretary, Dr. James L. Krieger, 85 Jefferson St., Hartford 6, Conn. Meets first Friday in February and April.

DALLAS-FORT WORTH RADIOLOGICAL SOCIETY
Secretary, Dr. Robert D. Moreton, 816 Medical Arts Bldg., Fort Worth, Tex. Meets monthly, third Mon-

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

day, at Greater Fort Worth International Airport at 6:30 P.M.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY
Secretary, Dr. Arch H. Hall, Harper Hospital, Detroit 1, Mich. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

EAST BAY ROENTGEN SOCIETY
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland, Calif.

EAST TENNESSEE RADIOLOGICAL SOCIETY
Secretary, Dr. J. Marsh Frere, Jr., 205 Medical Arts Bldg., Knoxville, Tenn. Meets in January and September.

EASTERN CONFERENCE OF RADIOLOGY
Secretary, Arrangements Committee, Dr. Luther W. Brady, 230 North Broad St., Philadelphia, Pa. Annual meeting to be announced.

EASTERN RADIOLOGICAL SOCIETY
Secretary, Dr. James F. Martin, North Carolina Baptist Hospital, Winston-Salem, N. C.

FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. Marvin V. McClow, St. Vincent's Hospital, Barrs and St. Johns Ave., Jacksonville 4, Fla. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Joseph C. Rush, 1800 Druid Rd., Clearwater, Fla.

GEORGIA RADIOLOGICAL SOCIETY
Secretary, Dr. George W. Brown, Griffin, Ga. Meets in spring and fall with Annual State Society Meeting.

GREATER MIAMI RADIOLOGICAL SOCIETY
Secretary, Dr. T. Hunter Pryor, Jackson Memorial Hospital, Miami 36, Fla. Meets monthly, third Wednesday, at 8:00 P.M. at Jackson Memorial Hospital, Miami, Fla.

GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS
Secretary, Dr. Harry I. Berland, St. Louis, Mo.

HOUSTON RADIOLOGICAL SOCIETY
Secretary, Dr. W. E. Kirkpatrick, 2708 Weslayan, Houston 27, Tex. Meets last Monday each month in fall winter and spring, Seminar Room, Doctors' Club of Houston.

IDAHO STATE RADIOLOGICAL SOCIETY
Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.

ILLINOIS RADIOLOGICAL SOCIETY
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

INDIANA ROENTGEN SOCIETY, INC.
Secretary, Dr. Richard A. Silver, 712 Hume Mansur Bldg., Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

IOWA RADIOLOGICAL SOCIETY
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Roger K. Wallace, Riley County Hospital, Manhattan, Kan. Meets in spring with State Medical Society and in winter on call.

KENTUCKY RADIOLOGICAL SOCIETY
Secretary, Dr. Lawrence A. Davis, 226 East Chestnut St., Louisville, Ky. Meets monthly on second Friday at Sheraton Hotel, Louisville.

KINGS COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. Abraham Berens, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

KNOXVILLE RADIOLOGICAL SOCIETY
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

LOS ANGELES RADIOLOGICAL SOCIETY
Secretary, Dr. Chester P. Bonoff, 1930 Wilshire Blvd., Los Angeles 57, Cal. Meets second Wednesday of month in September, November, January, March and June at Los Angeles County Medical Association Building, Los Angeles.

MAINE RADIOLOGICAL SOCIETY
Secretary, Dr. Charles W. Capron, Maine Medical Center, Portland, Me. Meets in June, September, December and April.

MARYLAND RADIOLOGICAL SOCIETY
Secretary, Dr. James A. Lyon, Jr., 7918 Springway Rd., Ruxton 4, Maryland.

MEMPHIS ROENTGEN SOCIETY
Secretary, Dr. Irving K. Ettman, Kennedy V.A. Hospital, Department of Radiology, Memphis 15, Tenn. Meets first Monday of each month at John Gaston Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. William D. Roberts, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

MID-HUDSON RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph Sorrentino, St. Francis Hospital, Poughkeepsie, N. Y. Meets 8:30 P.M., fourth Wednesday of each month September to May.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary, Dr. Abraham Marck, Mayfair Professional Bldg., Milwaukee 13, Wis. Meets monthly on fourth Monday, October through May, at University Club.

MINNESOTA RADIOLOGICAL SOCIETY
Secretary, Dr. Frank J. Anderson, 810 E. 27th St., Minneapolis 7, Minn. Meets three times annually, in fall, winter and spring.

MISSISSIPPI RADIOLOGICAL SOCIETY
Secretary, Dr. Jack K. Goodrich, University Medical Center, Jackson, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

MONTANA RADIOLOGICAL SOCIETY
Secretary, Dr. John M. Fritts, 1224 S. Higgins Ave., Missoula, Montana. Meets at least once a year.

NASSAU RADIOLOGICAL SOCIETY
Secretary, Dr. Herbert Kantor, 71 S. Oyster Bay Rd., Syosset, N. Y. Meets second Tuesday of the month in February, April, June, October and December.

NEBRASKA STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Richard Bunting, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEVADA RADIOLOGICAL SOCIETY
Secretary, Dr. George F. Fraser, Las Vegas, Nev.

NEW ENGLAND ROENTGEN RAY SOCIETY
Secretary, Dr. Robert E. Wise, 605 Commonwealth Ave., Boston 15, Mass. Meets third Friday of each month, October through April, at The Longwood Towers, Brookline, Mass. at 4:30 P.M.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

NEW YORK ROENTGEN SOCIETY
Secretary, Dr. James J. Nickson, Memorial Hospital, New York, N. Y. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M.

NORTH CAROLINA RADIOLOGICAL SOCIETY
Secretary, Dr. A. B. Croom, 624 Quaker Lane, High Point, N. C. Meets in the spring and fall each year.

NORTH DAKOTA RADIOLOGICAL SOCIETY
Secretary, Dr. John Jestadt, Depuy-Sorkness Clinic, Jamestown, N. D. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Anthony J. Tabacco, 621 Central Ave., Albany 6, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. Rob H. Kirkpatrick, 1219 28th St., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Northwestern Ohio Radiological Society
Secretary, Dr. Anthony F. Lalli, 421 Michigan St., Toledo, Ohio.

Ohio State Radiological Society
Secretary, Dr. Chapin Hawley, 927 Carew Tower, Cincinnati 2, Ohio. Annual Meeting: Dayton, Ohio, May, 1963.

Oklahoma State Radiological Society
Secretary, Dr. Simon Pollack, Utica Square Medical Center, Tulsa, Okla. Meets in January, May and October.

Oregon Radiological Society
Secretary, Dr. James A. Schneider, St. Vincent Hospital, Portland 10, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. John N. Burkey, 555 Dental Bldg., Seattle, Wash. Annual meeting: Seattle, Wash.

Pennsylvania Radiological Society
Secretary, Dr. Frederick R. Gilmore, Clearfield Hospital, Clearfield, Pa. Annual meeting: Bedford Springs Hotel, May 23–25, 1963.

Philadelphia Roentgen Ray Society
Secretary, Dr. Antolin Raventos, 3400 Spruce St., Philadelphia 4, Pa. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Marvin Brodie, 3459 Fifth Ave., Pittsburgh 13, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

Radiological Society of Greater Cincinnati
Secretary, Dr. Richard B. Mulvey, 2421 Auburn Ave., Cincinnati, Ohio. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of Hawaii
Secretary, Major Michael A. Lopiano, 784 Hoomalimali St., Pearl City, Hawaii. Meets third Monday of each month at 7:30 P.M.

Radiological Society of Greater Kansas City
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Andrew F. Giesen, Ochsner Clinic, New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

Radiological Society of New Jersey
Secretary, Dr. E. Arthur Kratzman, 912 Prospect Ave., Plainfield, N. J. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y. Annual meeting to be announced.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary, Dr. Richard P. Storrs, 2131 West Third, Los Angeles, Calif.

Redwood Empire Radiological Society
Secretary, Dr. Lee E. Titus, 164 W. Napa St., Sonoma Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Harry J. Pinsky, 386 Monroe Ave., Rochester 7, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting to be announced.

San Antonio-Military Radiological Society
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Tex. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
Secretary, Dr. Charles G. Campbell, 6673 Avenida Manana, La Jolla, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. Walter Coulson, San Francisco General Hospital, San Francisco 8, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Connecticut State Medical Society
Secretary, Dr. Wayne P. Whitcomb, Hospital of St. Raphael, New Haven, Conn. Meetings are held bimonthly.

Section on Radiology, Medical Society of the District of Columbia
Secretary, Dr. Martin A. Thomas, 1150 Connecticut Ave., Washington 6, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. Robert D. Sloan, University Medical Center, 2500 North State Street, Jackson 6, Miss. Annual meeting: Hotel Fontainebleu, Miami Beach, Fla., Nov. 12–15, 1962.

Section on Radiology, Southern Medical Association
Secretary, Dr. Seymour Ochsner, Ochsner Clinic, 3503 Prytania St., New Orleans 15, La. Annual meeting to be announced.

Section on Radiology, Texas Medical Association
Secretary, Dr. Frederick J. Bonte, University of Texas Southwestern Medical School, Dallas 35, Tex. Meets annually with the Texas Medical Association.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

Society for Pediatric Radiology
Secretary, Dr. Richard G. Lester, Box 151, Medical College Station, Richmond, Va. Annual meeting: Shoreham Hotel, Washington, D. C., Oct. 1, 1962.

Society of Nuclear Medicine
Secretary, Mr. Craig C. Harris, Oak Ridge National Laboratories, Oak Ridge, Tenn. *Administrator*, Mr. Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill.

Annual meeting: Queen Elizabeth Hotel, Montreal, Quebec, June 26–30, 1963.

South Bay Radiological Society
Secretary, Northern Section: Dr. John S. Wilson, 1515 Trousdale Dr., Burlingame, Calif.; Southern Section: Dr. A. C. Mitchell, 728 Cass, Monterey, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

Southern Radiological Conference
Secretary, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala. Annual meeting: Grand Hotel, Point Clear, Ala., Feb. 1–3, 1963.

Southwestern Radiological Society
Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

Tennessee Radiological Society
Secretary, Dr. B. M. Brady, St. Joseph Hospital, Memphis, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 402 Professional Bldg., 1216 Pennsylvania Ave., Fort Worth 4, Tex. Annual meeting: San Antonio, Tex., Jan. 25 and 26, 1963.

Tri-State Radiological Society
Secretary, Dr. John H. Marchand, Jr., Welborn Clinic, 420 Cherry St., Evansville, Ind. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Richard Y. Card, St. Mark's Hospital, Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Vermont Radiological Society
Secretary, Dr. John R. Williams, 160 Allen St., Rutland, Vt.

Virginia Radiological Society
Secretary, Dr. Powell G. Dillard, Jr., 715 Church Street, Lynchburg, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Robert H. Rosenberg, 7011 38th Ave., N.E., Seattle 15, Wash. Meets quarterly.

West Virginia Radiological Society
Secretary, Dr. Karl J. Myers, The Myers Clinic-Broaddus Hospital, Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. Edward T. Bello, Westchester Academy of Medicine, Section on Radiology, Purchase, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. Charles Benkendorf, 408 St. Francis St., Green Bay, Wis. Annual meeting each spring in various places.

Cuba, Mexico, Puerto Rico and Central America

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Julio Toriello, 11 Calle 2–37, Zona 1, Guatemala. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de El Salvador
Secretary, Dr. Rafael Vaga Gómez.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

Sociedad de Radiología y Fisioterapía Cubana
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

Sociedad Mexicana de Radiología, A. C.
Calle del Oro No. 15. México 7, D. F.
Secretary-General, Dr. E. Alvarez Hernández.
Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. Jorge Carreras Girard, Suite 504, Professional Bldg., Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
Secretary, Dr. Odilon Raymond, 5400 Blvd. Gouin. Quest, Montreal, Que., Canada. Meets four times a year.

British Institute of Radiology
Honorary Secretary, Dr. R. D. Hoare, 32 Welbeck St., London, W. 1, England. Meets monthly from October until May.

Edmonton and District Radiological Society
Secretary, Dr. S. C. Windle, 105 Northgate Bldg., Edmonton, Alberta, Canada. Meets first Tuesday of each month, October to May.

Faculty of Radiologists
Honorary Secretary, Dr. C. J. Hodson, 47 Lincoln's Inn Fields, London, W.C.2, England.

Faculty of Radiologists, Royal College of Surgeons in Ireland
Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green, Dublin 2, Ireland.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 11 Wimpole St., London, W. 1, England.

Canadian Association of Radiologists
Honorary Secretary, Dr. Robert G. Fraser, *Associate Honorary Secretary*, Dr. D. J. Sieniewicz, 1555 Summerhill Ave., Montreal 25, Que., Canada. Annual meeting to be announced.

Montreal Radiological Study Club
Secretary, Dr. F. McConnell, 1650 Cedar Ave., Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicale
General Secretary, Dr. Maurice Dufresne, 1560 Sherbrooke (East), Montreal, Que., Canada. Meets third Saturday each month.

Toronto Radiological Society
Secretary, Dr. Wallace M. Roy, St. Joseph's Hospitals 30 The Queensway, Toronto 3, Ont., Canada. Meet, second Monday of each month September through May.
College of Radiologists of Australia
Honorary Secretary, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.
Ateneo de Radiologia
Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional del Centenario, Santa Fe 1300, Rosario.
Colégio Brasileiro de Radiologia
Secretary-General, Dr. Tede Eston de Eston, Caixa Postal 5984, São Paulo, Brazil.
Sociedad Argentina de Radiología, Junta Central, Buenos Aires
Secretary, Dr. Edgardo O. Olcese, Santa Fé 1171, Buenos Aires. Meetings are held monthly.
Sociedad Bolivana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.
Sociedade Brasileira de Radiologia
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.
Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.
Sociedad Chilena de Radiología
Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.
Sociedad Colombiana de Radiologia
Secretary, Dr. Alberto Mejía Diazgranados, Carrera 13, No. 25–31, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.
Sociedad Ecuatoriana de Radiología y Fisioterapía
Secretary, Dr. Publio Vargas P., Casilla 1242, Guayaquil, Ecuador.
Sociedad Paraguaya de Radiología
Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.
Sociedad Peruana de Radiologia
Secretary, Dr. Luis Pinillos Ganoza, Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.
Sociedad de Radiologia del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41–110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.
Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.
Sociedade de Radiologia de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.
Sociedad de Roentgenologia y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.
Sociedad Venezolana de Radiología
Secretary-General, Dr. Rubén Merenfeld, Apartado No. 9362, Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.
Société Belge de Radiologie
General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets in February, March, May, June, October, November and December.
Société Française d'Electroradiologie Médicale, and its branches: Socété du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.
Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 8e, France.
Československá Společnost pro Roentgenologii a Radiologii
Secretary, Dr. Robert Poch, Praha 12, Šrobárova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.
Deutsche Röntgengesellschaft
Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut., Lagenbeckstr. 1, Mainz, Germany. Annual Congress: Baden-Baden, Germany, April 24–28, 1963.
Società Italiana di Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.
Nederlandse Vereniging voor Electrologie en Röntgenologie
Secretary, Dr. J. R. von Ronnen, Violenweg 14, den Haag, Netherlands.
Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.
Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear
Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.
Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

Asia

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.
Indonesian Radiological Society
Secretary, Professor Sjahriar Rasad, Taman Tjut Mutiah 1, Djakarta, Indonesia.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

GYNECOLOGY AND OBSTETRICS

COALE, G. B., III, RICHEY, L. E., and McGANITY, W. J. Localization of the placenta with intravenous aortography. *Am. J. Obst. & Gynec.*, May, 1962, *83*, 1150–1156. (From: The Departments of Obstetrics and Gynecology, and Radiology, University of Texas Medical Branch, Galveston, Tex.)

Accurate placental localization is important in vaginal bleeding in the third trimester of pregnancy. Vaginal examination under "double-setup" is the most direct method to rule out placenta previa if the fetus is mature. Auscultation, radioactive isotopic studies and roentgenographic methods using soft tissue technique and also contrast media have been employed to determine the placental site.

Angiographic studies for placental localization have not been widely utilized. Dos Santos, in 1931, described the appearance of the placental sinuses as well as the changes in the configuration of the uterine arteries using translumbar aortography. There have been several other studies by translumbar aortography for placental localization since that time. Fernström of Sweden, in 1955, published the results of studies done on 59 pregnant women with retrograde percutaneous iliac aortography to demonstrate the placenta. The placental sinuses were visualized as early as the eighth week of gestation. Nelson, in 1961, presented 260 cases in which retrograde aortography was used to show the placenta; intravenous angiography was employed by Ezes and Viallet in 1956.

The authors use a modification of the Goodlin method.

It consists essentially of: (1) a sensitivity test by injecting intravenously 1 cc. of the medium diluted with 10 cc. of normal saline; (2) determination of the circulation time—arm to tongue—using 5 cc. of dehydrocholic acid with the normal range being 6 to 12 seconds; (3) a No. 14 gauge needle or a Robb No. 12 cannula is inserted into an antecubital vein; (4) 80 to 100 cc. of renografin or renovist is injected in 2 to 3 seconds; (5) an anteroposterior roentgenogram is then made at the predetermined circulation time for pelvic aortography or the circulation time plus 2 seconds for placentography. A second injection can be done.

There were no untoward effects. The usual transient flushing occurred, and there was one case of transient vomiting. There were no fetal sequelae.

The authors studied 40 cases of which 36 were interpretable. There were 18 cases that were bleeding. The placentae were correctly localized in all but one case, giving an error of 2.8 per cent. The placenta in this case was a lateral placenta previa and was thought to be a normal implantation. One placenta was demonstrated at the tenth week of gestation. Separate placentae were demonstrated in a set of twins.

The conclusion is reached that intravenous placentography is a simple, safe and inexpensive method of determining the placental site with a minimum of special equipment and with a high degree of accuracy. The radiation exposure received by the patient is about the same as for a single anteroposterior roentgenogram of the abdomen and pelvis. It is emphasized that intravenous placentography is not a routine procedure and should be used in suspected cases of early placenta previa in the third trimester.—*Charles W. Cooley, M.D.*

McGOOGAN, L. S., LANGDON, R. M., OGBORN, R. E., COPLEY, J. S., and BURGIN, W. W. Radioactive triiodothyronine uptake by red cells in pregnancy. *Am. J. Obst. & Gynec.*, May, 1962, *83*, 1157–1166. (Address: 3568 Dodge Street, Omaha, Neb.)

The *in vitro* incorporation of thyroid hormonal components by red cells utilizing radioactive triiodothyronine (I^{131}-TRI) was described by Hamolsky in 1956. He found that there was a decrease in the uptake by the red cells in: (1) hypothyroidism, (2) pregnancy, and (3) in patients taking estrogens, cortisone or propylthiouracil. No appreciable effect on the red cell uptake was noted in: (1) patients taking iodine or mercury preparations, (2) anxiety states, (3) congestive heart failure, (4) hypertension, and (5) patients with enlarged thyroid glands (colloid goiter, nontoxic nodular goiter or thyroid carcinoma). There was an increase in the red cell uptake in: (1) hyperthyroidism, (2) in patients taking bis-hydroxycoumarin, and (3) in patients having nephrosis, hepatitis, cirrhosis of the liver or metastatic malignancy.

The authors aimed to determine if they could duplicate Hamolsky's work in a larger series of pregnant women in hopes that the information would be of clinical value. A base line for evaluation for the normal euthyroid population of reproductive age was determined in 50 normal men and 50 normal nonpregnant women. The mean uptake for men was 16.9 ± 2.54 per cent S.D. (1 standard deviation). Multiple determinations were made in the pregnancy series in the first trimester, in the third trimester, and in the postpartum period. Ninety-eight patients were tested in the first trimester group, 88 of the same women in the third trimester, and 86 of the remaining in the postpartum group. In the first trimester group, the mean uptake values, when grouped by weeks, showed an almost continual decrease from the fifth to the thirteenth week (16.0 per cent to 10.9 per cent). In the late second or third trimester, the uptake values, when grouped by weeks, were consistently below 1 S.D. of the normal mean. In 75 of the 86 patients in the postpartum period, the uptake values returned to within 1 S.D. of the normal mean. One patient was slightly below. The

remaining 10 patients had uptake values above 1 S.D. of the normal range (? rebound phenomenon). When grouped by weeks, the mean values returned to within 1 S.D. of the normal mean except in 4 cases.

The red cell uptake of I^{131}-TRI in the present series was not consistently depressed in early pregnancy in all cases and became significant only late in the first trimester (after 8 weeks), thus limiting its usefulness as an early pregnancy test. A high uptake beyond the eighth week could signify a pathologic condition in the patient or in the pregnancy itself. In 87 per cent of the 16 pregnancies that aborted, the uptake values were within the normal nonpregnancy means.

The authors detail their method of determining the uptake of I^{131}-TRI by the red cells. The physiology of the test is discussed.—*Charles W. Cooley, M.D.*

Genitourinary System

Gondos, Bela. Roentgenographic evaluation of the size and shape of the kidney. *M. Ann. District of Columbia*, Mar., 1962, *31*, 158–161. (Address: Assistant Clinical Professor of Radiology, Georgetown University School of Medicine; Chief Medical Officer, Department of Radiology, District of Columbia General Hospital, Washington 3, D. C.)

Significant enlargement of the kidney generally manifests itself as a "palpable mass" on physical examination, and usually is easily recognized on the roentgenogram. Slight and moderate enlargement, however, remains commonly ignored or unrecognized. This happens partly because of technical difficulties in demonstrating the kidneys and partly because of the unreliability of the measurements with the usual methods. Kleeberg and Dreyfuss called attention to the diagnostic and prognostic information obtained by the roentgen evidence of a contracted kidney in chronic glomerulonephritis and hypertensive vascular disease. Whenever the demonstration of a decreasing kidney size was made, a corresponding deterioration of the kidney function was also observed. This observation is particularly significant in cases of acute renal insufficiency, as emphasized by Olsson. In the late phase of chronic glomerulonephritis a small kidney may indicate the presence of a contracted kidney as compared with a kidney of normal or increased size in the acute stage of the disease. Thus the demonstration of the kidney size in uremia may make the differential diagnosis possible between an acute exacerbation of chronic glomerulonephritis and acute glomerulonephritis.

The kidney image on the roentgenogram is magnified according to the principle of central projection. This magnification amounts approximately to 8 to 10 degrees in a person of average size when the generally accepted techniques are employed. This is inherent to the procedure and is generally known. Another and less appreciated source of distortion of the kidney image results from rotation of the kidney.

Rotation may occur around the transverse axis, which produces a shortened kidney image with a normal width. Slight rotation with the upper pole tilted posteriorly is commonly present in normal persons. In cases of ptosis or of abdominal (both intraperitoneal and retroperitoneal) masses rotation may reach a marked proportion; this results in significant distortion of the kidney image.

A more common type of rotation is that around the longitudinal axis. There may be no rotation when the hilus looks medially. This is the position which produces the widest possible transverse diameter of the kidney image. Most commonly with the patient supine a rotation of variable degree is found with the hilus looking medially and anteriorly. This rotation results in a narrower kidney image. The rotation and the distortion of the kidney image are eliminated or significantly reduced after the patient is placed in the erect or prone position. This change in size and shape is the result of a rotation with the hilus looking medially. Because of the rotation described, prone position is believed to be more adequate for evaluation of the size and shape of the kidney than the generally employed method with the patient in the supine position.

For a determination of the length and width of the normal kidney image on the roentgenogram, measurements in 100 persons without significant kidney disease both with the patient supine and prone, were taken. The transverse diameter was measured at the level of the hilus where the convexity is the most prominent; the medial end of the transverse diameter was determined by a line drawn through the most prominent points of the medial contour above and below the hilus. The measurements show that the transverse diameter is considerably wider when it is taken with the patient prone as compared with that taken in the supine position. This is the result of a decrease or absence of rotation when the patient is prone. For this reason, measurements in this position approximate the anatomic values better than those taken in the supine position.

The figures given intend to provide a standard of measurements of the kidney image for comparison purposes. In any evaluation of the size and shape of the kidney, significant rotation either around the transverse or the longitudinal axis should be ruled out. If the presence of rotation is overlooked, an incorrect diagnosis of hypoplastic or contracted kidney or that of a cyst or tumor may be made.—*Bela Gondos, M.D.*

Gondos, Bela. Urographic studies in abdominal masses: the diagnostic value of kidney rotation. *Radiology*, Feb., 1962, *78*, 180–186. (From: The Department of Radiology, D. C. General Hospital, Washington, D. C.)

There have been many reports in the literature well documenting the fact that renal displacement cannot be used as a diagnostic sign for the differen-

tiation between intra- and retro-peritoneal masses. Rotation, however, commonly accompanies displacement of the kidneys and it may be the earliest manifestation of an abdominal space-occupying process. The purpose of this paper is to suggest that rotation of the kidneys with or without obvious displacement can be utilized in localization of abdominal masses.

A mass posterior or medial to the kidney encroaches upon the space between the psoas muscle and kidney and may displace the kidney laterally and rotate the hilus anteriorly. If there are bilateral masses the symmetric roentgen findings suggest the presence of lymphoma or metastatic tumors of the testis. If the mass is located adjacent to one of the extremities of the kidney rotation around the sagittal axis may occur. This has been observed in solitary cysts of an extremity, in adrenal tumor, and in a double kidney with hydronephrosis involving the upper part of the duplication.

A mass anterior to the kidney will rotate it with the hilus looking medially. If this rotation cannot eliminate the space-occupying "force," due to the large size of the mass, there will be compression of the kidney in the sagittal diameter. Large intra-abdominal tumors, masses of the pancreas, and solitary cysts and tumors of the kidney will give this appearance.

A mass lateral to the kidney, if large enough, will displace the kidney medially beyond the shadow of the psoas muscle and will rotate the kidney so that the hilus faces posteriorly. Very large retroperitoneal masses may displace the kidney beyond the midline.

With masses proximal and distal to the kidney, the space available for it is encroached upon in the vertical direction and rotation occurs around the transverse axis, with the inferior pole generally moving anteriorly. This is seen in tumors of the adrenal, tumors and solitary cysts of the kidney and retroperitoneal abscess. It is commonly associated with enlargement of the liver, spleen, and the gallbladder.

These specific patterns of rotation and displacement, however, are seen only occasionally. More commonly there is a combination of the different types of rotation. Many factors enter, leading to some inconsistency in these patterns. Some of these factors include: body habitus, size and rotation of adjacent organs, tone of muscles in the abdominal wall, positional changes of the patient (erect, supine, prone, etc.) ptosis and scoliosis. The physical factors operating to produce these patterns were found to be similar in the presence of both intraperitoneal and retroperitoneal masses and there was no essential difference in this respect whether or not the mass was attached to the kidney.—*Donald N. Dysart, M.D.*

GHORAB, M. M. A. Ureteritis calcinosa: complication of bilharzial ureteritis and its relation to primary ureteric stone formation. *Brit. J. Urol.*, Mar., 1962, *34*, 33–43. (Address: M. M. A. Ghorab, Assistant Professor of Urology, Faculty of Medicine, Alexandria, U.A.R.)

The author states that this complication of bilharzial ureteritis has never before been mentioned by other writers. The roentgenograms reveal punctate calcification of one or both ureters more commonly in the pelvic than in the lumbar segments. In early cases the lesion is in the form of minute discrete areas of calcification involving a short segment of ureter but in advanced cases the calcified ureter is thick, 1 to 2 cm. in diameter, and in some cases the whole ureter and even the pelvis and calyces are involved. The individual areas of calcification vary in diameter from a pin head to a few millimeters or even more and sometimes take the shape of irregular ureteric stones. In some cases the calcified areas are conglomerate with little space between them, while in others they are dispersed along the course of the ureter a few centimeters apart.

Intravenous pyelography shows good function of the kidney on the affected side, whether unilateral or bilateral, with no dilatation of the calyces. There is usually no evidence of stagnation of the contrast medium in the ureters. In other parts of the ureters not affected by ureteritis calcinosa, multiple small filling defects are shown suggesting the presence of ureteritis cystica.

Patients suffering from this condition usually complain of repeated attacks of renal pain on one or both sides, varying from a dull ache to agonising attacks of ureteric colic. These usually end by the passage of a number of small concretions. In cases followed sufficiently long the colic becomes less severe and less frequent and ultimately disappears spontaneously.

Cystoscopic examination invariably reveals a bladder with active bilharziasis or traces of past bilharzial infection.

The treatment adopted aims to dislodge the concretions from the ureteric wall with the removal of as many stones as possible. Ureteric catheterisation is helpful when the catheters can be passed up the ureters. When this procedure cannot be performed, ureterolithotomy is necessary. This procedure discloses extensive periureteric adhesions and shows the ureter itself to be very much thickened.

Most of the calculi passed by these patients and many removed at operation have very peculiar and characteristic shapes. There is a stump of hard brownish material containing an iron pigment and usually not more than 2 mm. in diameter. In addition, there is a cap formed mostly of calcium oxalate crystals sometimes smaller than the brownish stump but often much larger up to 0.5 cm. or more in diameter.

The case reports of 10 such patients are included.—*Arthur E. Childe, M.D.*

KAUFMAN, JOSEPH J. Medication simulating bladder stones. *Radiology*, Feb., 1962, *78*,

227–228. (From: The Department of Surgery, Division of Urology, University of California Medical Center, Los Angeles, Calif.)

A case is presented to illustrate the fact that heavy-metal-containing vaginal suppositories may cast roentgenographic shadows closely simulating bladder calculi. After a negative cystoscopy, two shadows roentgenographically interpreted as being "in the bladder" were found to be due to Baculin vaginal tablets, containing diiodohydroxyquinoline.

Other vaginal suppositories which contain sufficient iodine, silver, mercury or arsenic to cast dense shadows on roentgenograms include: Floraquin (diiodohydroxyquin), Lycinate (diiodohydroxyquin), Picragol (silver picrate), Quinettes (diiodohydroxyquinoline), Triserts (phenyl mercuric acetate), and Vioform (iodochlorohydroxyquin).

Where confusion exists, a true lateral roentgenogram should show the vaginal tablets posterior to the bladder.—*Ralph Bowman, M.D.*

Kill, F., and Aukland, K. Renal tubular permeability to radioactive sodium, bromide and iodide isotopes. *Scandinav. J. Clin. & Lab. Invest.*, 1962, *14*, 124–131. (From: The Institute for Experimental Medical Research, University of Oslo and Medical Department VII, Ullevål Hospital, Oslo, Norway.)

The primary purpose of this study was to determine if the difference in the clearance rates of iodides and bromides might mainly be due to differences in passive permeability of the proximal tubules to these anion species. The proximal tubules can be considered as the more permeable segment, both to water and anions. The distal tubules and proximal portions of the collecting ducts are highly permeable to water only in the presence of antidiuretic hormone. The antidiuretic hormone in physiologic concentrations does not affect the transport of sodium and its anions.

Stop-flow studies were done on 10 dogs according to the procedure previously described by the authors in 1960. Na^{24}, Br^{82} or I^{131} were injected together with glomerular indicators after clamping the ureteral catheter for 12 minutes. The filtration indicators were used in order to determine whether the radioactive isotopes had reached the tubular fluid through the tubular wall or through the glomerular membrane. The studies were repeated after 20 minutes additional intravenons administration of the isotope at which time the plasma concentrations were nearly constant.

The studies indicated that I^{131} was added to the fluid in the proximal tubules through the tubular wall. The proximal tubules and possibly the distal tubules were found to be more permeable to Br^{82} than to I^{131}. The stop-flow excretion pattern for Br^{82} was nearly identical to that of Cl, but the concentration index for Br^{82} was lower than for Cl during free-flow and in all stop-flow portions. The Na^{24} excretion pattern was similar to that of Br^{82}.

The above data suggest that the proximal tubules of the dog are highly permeable to sodium and that the permeability to the sodium and bromide ions is grossly of the same magnitude. The permeability to the iodide ions is much lower, but is of the same order as the tubular permeability to radioactive urea.

There is a general discussion about renal tubular absorption and of the significance of passive flux of sodium under changing conditions of concentrations, electrical potential and colloidal osmotic pressure.—*Charles W. Cooley, M.D.*

Skeletal System

Hassenhuttl, Kurt. Osteopetrosis: review of literature and comparative studies on case with twenty-four year follow-up. *J. Bone & Joint Surg.*, Mar., 1962, *44A*, 359–370. (From: The New Jersey Orthopaedic Hospital and the Orthopaedic Service of Orange Memorial Hospital, Orange, N. J.)

This is a detailed report of a 24 year follow-up on a case of osteopetrosis first diagnosed at the age of 3. His parents were third cousins. No other cases of osteopetrosis were discovered in the living relatives.

The initial roentgenograms are presented and these show the characteristics of a moderately severe osteopetrosis. During the next 24 years the bone changes progressed and the patient had multiple (33) fractures, always caused by trivial trauma. The time of healing was not delayed except when there were repeated fractures through the same area. The transverse bands of density in some tubular bones were not associated with fractures and are considered to be "secondary to faulty bone development."

Physical development progressed normally. He had no involvement of liver, spleen or lymph nodes. In addition to all the usual bony changes, he developed optic atrophy due to encroachment of bone on one optic foramen beginning at the age of 5. He also had extreme bilateral coxa vara without evident preceding fracture, and marked deformity of the right forearm following 15 fractures.—*Martha Mottram, M.D.*

Mankin, Henry J., and Brower, Thomas D. Bilateral idiopathic aseptic necrosis of the femur in adults: "Chandler's disease." *J. Hosp. Joint Dis.*, Apr., 1962, *23*, 42–57. (From: Orthopedic Surgery, University of Pittsburgh, Pittsburgh, Pa.)

Aseptic necrosis of the head of the femur in adults is usually a sequela of a fractured neck of the femur or dislocation of the hip joint. More rarely aseptic necrosis occurs spontaneously without trauma. The cause of this spontaneous necrosis may be attributed

to caisson disease; hemoglobinopathy; external irradiation, bone seeking isotopes; Gaucher's disease; prolonged administration of corticosteroids; trauma about the trochanter; or infection. There have been reports of cases of unilateral or bilateral aseptic necrosis in which no etiologic agent could be found. Chandler and Phemister were most prolific in this regard, and the best descriptions of the entity and discussions of its etiology appear in their publications.

The authors state that the purpose of the present study is to define the features of "Chandler's disease," on the basis of 5 new cases observed in the last 4 years (bringing the total reported cases to 27 since 1929). Some new theories regarding the etiology are briefly discussed, but very little can be added to the original suggestions of Chandler and Phemister in their discussions of 25 years ago.

The authors conclude that primary idiopathic aseptic necrosis of the femoral heads in adults is a rare disease affecting otherwise healthy men in the third, fourth or fifth decade. The condition occurs bilaterally in over 60 per cent of the cases and may be more prevalent in alcoholics. Pain is the outstanding complaint and is of gradual onset, always progressive and eventually incapacitating the individual.

The roentgenograms characteristically demonstrate diffuse necrosis of the femoral heads. The histologic examination is also fairly typical. The 5 personal cases and a review of the 22 cases from the literature contributed no data which could either substantiate or contradict any of the more reasonable theories of etiology.—*Peter C. Truog, M.D.*

HARRIS, W. H., DUDLEY, H. ROBERT, JR., and BARRY, R. J. The natural history of fibrous dysplasia: orthopaedic, pathological, and roentgenographic study. *J. Bone & Joint Surg.*, Mar., 1962, *44A*, 207–233. (From: The Departments of Orthopaedic Surgery, Pathology, and Radiology of the Harvard Medical School and the Massachusetts General Hospital, Boston, Mass.)

During the last 30 years, 90 patients at Massachusetts General Hospital were diagnosed as having fibrous dysplasia. Cases without available roentgenograms were discarded and there remained 37 classified as polyostotic fibrous dysplasia (20 with histologic confirmation) and 13 as monostotic fibrous dysplasia, all biopsy-positive. Non-ossifying fibroma, unicameral bone cyst and aneurysmal bone cyst must be differentiated from monostotic fibrous dysplasia and metabolic bone disease must be excluded in cases of polyostotic fibrous dysplasia. All the cases originally diagnosed at Massachusetts General Hospital were re-evaluated and 28 per cent of these were excluded because of incorrect diagnoses.

Polyostotic Fibrous Dysplasia. In 70 per cent of the patients with polyostotic fibrous dysplasia a limp, leg pain or fracture was the initial symptom; 25 per cent of the females had vaginal bleeding as the initial complaint; and 4 of 5 were under 4 years of age. The most common physical deformity was leg length discrepancy often due to "Shepherd's Crook" deformity of the femur.

There was no correlation between the alkaline phosphatase level and the extent of bone involvement although it was elevated in one-third of these patients.

The clinical course varied markedly in the 37 patients. In general, when the changes developed early in life the progression was marked and the prognosis poor. Puberty had no beneficial effects on the course of the disease. Three died of extensive progressive fibrous dysplasia with debilitation. One died of osteogenic sarcoma and one of myxofibrosarcoma with metastases. These patients previously had local irradiation. At the time of this report 14 patients were asymptomatic and active, 12 had pain or limp and were functionally active. Two patients had been asymptomatic 40 and 50 years.

The most common form of progression of these lesions is an increase in deformity, often associated with extension of existing lesions. Progression occurred in this series both before and after puberty. Of 26 patients with complete skeletal surveys 50 per cent had demonstrable extension of their disease. About 30 per cent had new lesions appear, in all but one, after puberty. Only 2 patients had roentgenographic evidence of improvement of a lesion but at the same time other lesions in these patients showed stability or progression.

The typical roentgen appearance of so-called cyst is caused by thinning of the cortex by a fibro-osseous mass which only occasionally contains degenerated zones with true cyst formation. The multilocular appearance is created by the scalloped pattern of endosteal erosion and residual incomplete septa. The ground glass appearance is due to superimposition of multiple thin calcified trabeculae. In some cases normal tubulation did not occur and the diaphysis remained wide and in others, re-expansion of the diaphysis occurred due to local involvement. Bone deformities such as coxa vara, Harrison's grooves bowing, and intrapelvic acetabular protrusion were frequent. Fibrous dysplasia may stimulate growth, as 5 patients with leg length discrepancies had disease only in the longer extremity. Advanced skeletal age was present in about one-sixth of the patients diagnosed before puberty and 2 had epiphyseal lesions. A unilateral pattern may occur but is not common. The femora, tibiae and pelvis are the most frequently involved bones.

The skull showed increased density of the base and thickening of the occiput in about 50 per cent of cases. The sphenoid and frontal sinuses were frequently obliterated. Displacement of one orbit inferiorly and laterally was a common deformity.

Fractures may occur after minor trauma, are seldom displaced and healing is usually prompt. Non-

union occurred twice in over 125 fractures. Surgical intervention was advised only with non-union of fracture, femoral shaft fracture in adults, and significant or progressive pain or deformity. Autogenous bone grafts appeared to incorporate more readily than homogeneous bone.

This histologic pattern is reviewed and in cases with multiple biopsies, the basic histologic pattern did not vary over intervals as long as 13 years.

Monostotic Fibrous Dysplasia. Thirteen cases are presented: 6 with craniofacial, 5 with rib, 1 with vertebral and 1 with tibial involvement. Only 1 patient had a cafe-au-lait spot.

In the 6 patients with craniofacial involvement 5 complained of a mass. The development of new lesions in other areas was not observed in the follow-up period which averaged 19 years. In 5 patients the lesions increased in size despite curettage or radical resection.

The rib lesions were all incidental findings. The average age was 23.

The gross appearance of these lesions was similar to that of cases of polyostotic fibrous dysplasia except that no cartilaginous or fluid filled cysts were found. In spite of large amounts of histologic new bone formation over a 5–10 year period, none of the lesions showed increased sclerosis histologically or roentgenographically. Repeat biopsies showed only minor changes. Whenever cartilaginous islands were found they were at the site of previous trauma; chondrosarcoma has not been reported in fibrous dysplasia.

No diagnostic criteria can be used to separate monostotic from polyostotic fibrous dysplasia. Monostotic lesions did not become polyostotic.—*Martha Mottram, M.D.*

Peterson, J. C. Metaphyseal dysostosis: questionably a form of vitamin D-resistant rickets. *J. Pediat.*, May, 1962, *60*, 656–663. (From: Milwaukee Children's Hospital, Milwaukee, Wis.)

Two cases of metaphyseal dysostosis treated with large doses of vitamin D with good results are presented. Previous authors have warned against this type of therapy.

The first case was a 7 year old boy with a waddling gait, ankle inversion and pronation of the foot. The initial laboratory studies were normal. Roentgenograms of the long bones revealed a coarse atrophic structure with epiphyseal cartilage irregularity and cystic changes in the metaphyses. The changes were most marked in the right distal tibia. Early slipping of the capital femoral epiphyses was present. The skull was normal.

Vitamin D_2 therapy was begun with a progressive increase in the dose to a maximum of 72,000 U daily after 3 months. Four months after initiation of therapy, marked healing was noted roentgenographically. After 10 months, healing was complete. The blood chemical studies were normal with no evidence of vitamin D toxicity at any time.

The second case was a 13 year old girl seen initially at 2 years of age because of dwarfism and bowing of the legs. Metaphyseal radiolucent zones, coxa vara, and femoral bowing were noted on the roentgenograms at age 2. The laboratory studies were normal. Repeat roentgenograms at age 13 showed changes similar to the previous case. Vitamin D_2 administration was begun, after femoral osteotomies to correct the coxa vara, with prompt improvement in the bone changes. The improvement was progressive for the 7 months of observation.

The family of the second patient had a history of dwarfism and waddling gait through 4 generations. The first case had no definite family history. The disease is thought to be transmitted as a dominant characteristic.

The site of action of vitamin D in this disease is not clear, but it does not conform to the commonly accepted physiologic actions. The author postulates a direct effect on the deposition of apatite crystals in the osteoid.

Certain cases of metaphyseal dysostosis may represent a variant of vitamin D-resistant rickets but more than one entity is apparently included since some reported cases do not respond to extremely large doses of vitamin D. Further studies on calcium and phosphorus metabolism are suggested.—*Barry Gerald, M.D.*

Ledoux-Lebard, G., Pellegrino, A., and Heitz, F. (Paris, France.) Mycose osseuse. (Osseous mycosis.) *J. de radiol., d'électrol. et de méd. nucléaire*, Jan.–Feb., 1962, *43*, 48–50.

Mycotic or fungus disease is frequent in West Africa and often results in the so-called Madura foot or mycetoma. These are inflammatory tumors caused by tissue reaction to the fungus which is usually introduced through a break or abrasion of the soft tissues. It is very likely that the fungus grows as a saprophyte on thorny or spiny bushes which flourish on soil of clay or sand. People walking amidst these bushes with bare feet suffer abrasions and the result is the classic Madura foot. Rarely does this involve the thigh or other parts of the lower extremities at a higher level.

The authors report a case of a 30 year old male with the complaint of a swollen knee with multiple fistulous tracts and a yellowish stringy discharge. Four years previously he fell in a large cactus bush and a thorn penetrated the anterior aspect of his knee. Only part of the thorn was removed and the tip remained embedded deep in the soft tissues. Swelling and disability developed, complicated eventually by multiple fistulous tracts. Roentgenographic examination revealed multiple cavitations varying in size from a pea to a prune, presenting the aspect of a

multilocular cystic lesion of the proximal tibia. They were surrounded by relatively dense bone, with cortical interruption at the extreme anterior and posterior aspect. The soft tissues at the knee were appreciably thickened. Based on these roentgen findings and the history, a diagnosis of mycotic or fungus disease was made.

At surgery the soft tissues were found to be studded with caviar like black granules around the knee. Bony cavitations and destruction in the proximal tibia corresponded to the roentgenologic findings. The destruction was so extensive as to necessitate amputation above the knee.

This case is considered striking in that the area involved is at a considerably higher level than usual. The feet and to a lesser extent the hands are frequently involved. The structural changes and cavitations may be so extensive, especially in the tarsal and metatarsal areas, that the original outline of the bone may be completely lost. Surrounding the areas of bone destruction there is often appreciable bone reaction with a condensation of bone.

In this type of disease bony involvement is usually secondary to the soft tissue infection.—*William H. Shehadi, M.D.*

Rogers, Donald L., and Benson, Thomas E. Familial Letterer-Siwe disease: report of case. *J. Pediat.*, Apr., 1962, *60*, 550–554. (Address: Chairman, Pediatric Section, Methodist Hospital, Indianapolis, Ind.)

Only 6 cases of familial Letterer-Siwe disease have been described in the literature. The authors present 2 additional cases in the same family, and give a brief résumé of the other reported instances of familial Letterer-Siwe disease. The most outstanding findings were anemia, thrombocytopenia, hepatosplenomegaly, and the presence of histiocytes in the reticuloendothelial system. Both patients, one age 12 days and the other age 2 months, showed an erythematous skin rash and marked anemia with rapid deterioration.—*Francis P. Shea, M.D.*

Francis, Kenneth C., Hutter, Robert V. P., Phillips, Ralph K., Eyerly, Robert C., and Schecter, Lawrence. Osteogenic sarcoma. *New England J. Med.*, Apr., 1962, *266*, 694–699. (From: The Bone Service of the Department of Surgery, The Department of Radiation Therapy and the Department of Pathology, Memorial Hospital for Cancer and Allied Diseases, and the James Ewing Hospital of the City of New York, N. Y.)

This is a most interesting report of a 5 year survival of a case of osteogenic sarcoma with subsequent metastases. The patient was an 8 year old boy who had had symptoms of pain in the femur for 3 months and a mass for 1 month. Roentgenograms showed a destructive lesion with pathologic fracture. This was biopsied and osteogenic sarcoma diagnosed. Disarticulation was refused by the parents. Irradiation was administered to the primary tumor with 250 kv. and 1,000 kv. to a total tumor dose of 5,300 r in 7 weeks.

Ten months later he returned and a re-check chest roentgenogram, which had previously been normal, showed multiple metastases to the left lung, with resulting pain, cough and dyspnea. Irradiation to the left chest was begun with 1,000 kv. After the third treatment the patient became acutely ill with a high fever and the therapy was interrupted. One week later it was resumed and a total dose of 1,728 r was given to the left lung, with a striking result; the metastases have disappeared and after 3 months the lung was normal roentgenographically.

Seven months later he developed a pleural effusion and metastases to the right lung. These have also disappeared after minimal (2,142 r) irradiation. Five months later (3 years and 5 months after the original diagnosis) the patient fell and fractured the femur through the original tumor site. The biopsy showed active osteogenic sarcoma.

Disarticulation was performed and the patient has been free of disease, almost 2 years later: 5 years and 4 months after the original biopsy.—*George L. Sackett, Jr., M.D.*

Nobel, W. (Greenfield, Mass.) Posterior traumatic dislocation of the shoulder. *J. Bone & Joint Surg.*, Apr., 1962, *44A*, 523–538.

The diagnosis of posterior dislocation of the shoulder is so frequently missed that the injury has been called "a diagnostic trap." Besides its rarity, there are several reasons for this appellation. The clinical signs may be minimal or may simulate other shoulder disorders but the major difficulty lies in the paucity of roentgenographic evidence of abnormality when the joint is examined by routine methods.

Typically, in the roentgenographic examination of the shoulder, only a single roentgenogram in the anteroposterior projection is obtained. In this projection, the signs of dislocation are usually very elusive. In the subacromial type, the appearance simulates the normal and in the rare posterior subglenoid type, this view does not permit differentiation from the deformity produced by anterior or central dislocation. Diagnosis often depends upon knowledge of the subtle abnormalities which may be present. Normally, the medial part of the head of the humerus is superimposed upon the glenoid fossa. The image of the overlapping structures forms an elliptic or half moon shadow which reaches down to the inferior border of the fossa. However, in the event of posterior dislocation, superimposition may no longer be present and the elliptic shadow is absent. The head seems to ride high in the glenoid fossa and the lower part of the fossa is empty. Occasionally, displacement is such

that a gap is visible between the fossa and the head. Sometimes, there is a grooved defect in the anterior aspect of the humeral head—an indented compression fracture caused by the impact of the posterior glenoid rim against the spongious humeral head. This sign will be missed, however, unless the anteroposterior roentgenogram is taken in rather marked internal rotation. Occasionally, with posterior dislocation, the humeral head and glenoid shadow do appear to overlap but abnormality is suggested by the fact that, in its extra-articular position, the medial margin of the head is no longer sharply defined but is indistinctly delineated; in addition, the level of the overlap is near the upper rim of the glenoid. None of the changes seen on the anteroposterior roentgenogram is pathognomonic since most can be reproduced by holding the arm across the chest or supporting the elbow in a sling.

Therefore, it is the axillary roentgenogram that establishes the definitive diagnosis and it should always be obtained in the presence of puzzling clinical findings or if suggestive signs are noted on the anteroposterior roentgenogram. It would seem to be the only method of differentiating the posterior subglenoid deformity from dislocations which occurred by the anterior or inferior route. An appreciation of the mechanism and course is important to successful correction. Roentgenograms in the axillary projection are best obtained if the "mid-glenoid line" is constructed by bisecting the glenoid fossa in the coronal plane. After central subglenoid dislocation, the humeral head is bisected by this line and the relationship of the humeral head to this line will indicate anterior or posterior position.

The author discusses the treatment of the injury emphasizing that prompt recognition and reduction of acute dislocations are essential because prognosis deteriorates with delay. The case histories of 10 patients are presented and constitute an appreciable addition to the rather scanty clinical data on this condition. The majority of the patients in this series suffered recurrent episodes of dislocation and the anatomic abnormalities responsible for recurrence are discussed. They consist of detachment or relaxation of the posterior part of the capsule, detachment or erosion of the posterior labrum, a grooved defect in the anterior of the humeral head caused by contact with the hard glenoid rim at the time of the initial injury which eliminates the normal anterior protuberance and allows the head to slide more easily over the labrum. In addition, a congenital defect of the glenoid fossa may exist. To these abnormalities, a fifth pathologic condition is added: congenital laxity of the shoulder joint. This may be familial and is sometimes seen in association with other abnormalities in Ehlers-Danlos syndrome and Marfan's syndrome. Since these are rare, it might be well to investigate cases of recurrent dislocation for evidence of possible fibrous tissue disease.—*Jack Reynolds, M.D.*

MacDonald, F. R. Intra-articular fractures in recurrent dislocation of the shoulder. *J. Canad. A. Radiologists*, Mar., 1962, *13*, 1–8. (From: Royal Victoria Hospital, Montreal, Quebec, Canada.)

Intra-articular fracture of the head of the humerus is a common occurrence in recurrent dislocation of the shoulder. The fracture is of the compression type and is found about the posterolateral notch on the head of the humerus. It is caused by pressure from the glenoid rim on the head of the humerus in the final locked position of the dislocation. Healing occurs with the formation of fibrocartilage covering this area and leaves a notch or groove in the head of the humerus.

Intra-articular fracture is seldom recognized since routine roentgenography of the shoulder very often does not demonstrate the groove or fracture. Surgical repair is commonly made through an anterior approach and the groove being posterolateral is often overlooked.

The floor of the defect usually appears as a denser layer of bone substance on the posterolateral portion of the head where the articulating portion joins the greater tuberosity. The defect runs in the longitudinal axis from the pole of the head down to the anatomic neck.

The author reviewed the case histories of 55 patients with recurrent dislocation of the shoulder. The defect can be visualized in 100 per cent of patients with recurrent anterior dislocation if special roentgenographic techniques are used. Five different roentgenographic projections are necessary to visualize the defect. These are described in the article with illustrations of these positions and the subsequent roentgenograms obtained. The clinical significance of this fracture is unknown.

The original article should be read by those not familiar with this condition.—*Frank J. Rigos, M.D.*

Wiltse, L. L. (Long Beach, Calif.) The etiology of spondylolisthesis. *J. Bone & Joint Surg.*, Apr., 1962, *44A*, 539–560.

After an extensive review of the facts and theories concerning the nature of spondylolisthesis, particularly that form of the disorder associated with a defect at the pars interarticularis, the author discusses his concept of the etiology. It is proposed that there are two causative factors: (1) an hereditary dysplasia in the cartilaginous model of the arch of the afflicted vertebra; and (2) strain on the pars interarticularis in the lower lumbar spine due to the erect stance and lumbar lordosis peculiar to man.

In developing this thesis the topic is discussed in depth and certain facets are emphasized. The hereditary nature of the disorder has been suspected and the author's studies offer confirmatory evidence. The families of 36 patients were examined roentgenographically. Of the 101 individuals so studied, 26

were afflicted. The mechanism of inheritance is not clear, but may be the result of a single recessive gene with incomplete penetrance.

The site of the lesion was examined as a pathologic specimen in 15 cases and the author's findings were in general accord with those of others. The pathologic anatomy varied with the size of the defect. A wide gap was bridged with fibrous tissue resembling normal ligaments. When the bone ends were close, they appeared smooth and blunt, and, occasionally, hyaline cartilage marked the margins. In others, the bone ends tapered so that the pars interarticularis was attenuated and the bone ends sharply pointed. In some, fibrocartilage proliferated at the site of the hiatus to the degree that it appeared to press on adjacent nerve roots.

It was shown that the osseous tissue about the defect is vital and metabolically normal by determining, with ultraviolet microscope that the uptake of tetracycline at the line of defect was the same as that in the cortex in the spinous process in a surgical specimen.

It has been proposed by some that in the presence of spondylolysis the occurrence and degree of slipping are controlled by the shape of the centrum of the involved segment, since in patients with spondylolisthesis the shape of the centrum is often markedly trapezoid and being wedge shaped, might more easily slip forward with weight bearing. Others have noted that, with severe spondylolisthesis, the sacral plateau is not flat, but dome shaped, and thus unstable.

The author feels that these abnormalities of shape and other associated disorders such as increased lumbar lordosis are secondary signs and are, in a sense, the result and not the cause of the slipping. Earlier data in this regard are derived from observations in the adult spine, but the lesion has its origin in childhood and measurements obtained at that age, when the initial lesion appears, show no abnormality in the shape of the elements about the lumbosacral region. Once slipping has begun, involuntary pelvic flexion occurs and with the altered posture and weight bearing changes are produced in the shape of the regional bony elements. After spondylolisthesis is clearly underway, the discovery of an associated severe wedging of the centrum and a perpendicular sacrum with a dome shaped top is of some prognostic value in the child under ten. These signs suggest that the ultimate displacement will be very marked. The cause and course of displacement "seem predestined" and, as yet, unknown.

Many theories of etiology have been advanced but most have, in whole or part, been discarded. Careful dissection of fetuses and stillborns has failed to produce evidence of a developmental abnormality in the form of separate ossification centers in the pars interarticularis or of a defect due to birth fracture. The absence of the disorder at birth and its increased incidence up to adulthood suggest that it is an ordinary fracture which for some reason, fails to heal. This seems unlikely when it is noted that proven fractures of the area show the normal reparative process. It has been proposed that the pars interarticularis may be "pinched" between the facets of the elements above and below. This appearance is sometimes simulated in roentgenograms of the abnormal adult spine, but roentgenograms in childhood, at the time of onset, show a normal special relationship and thus no impingement.

In supporting the hypothesis that spondylolisthesis is the result of localized dysplasia and stress, some of the peculiarities of the disease are reviewed: the defect occurs only in man who, alone, has a true upright stance and lumbar lordosis. It is not present at birth. Slipping, if it occurs, is seen before 20. The bone adjacent to the defect is normal and shows no evidence of aseptic necrosis or cystic change. The incidence of the defect in America is about 5 per cent. It is more than twice as common in the male. In patients with the disease there is an increased incidence of spina bifida and idiopathic scoliosis. Although the disease is familial, the segment involved varies and may be multiple; the site subjected to the greatest stress or with the greatest dysplasia develops a defect. The exact nature of the dysplasia is not clear but is thought to be related to a localized imbalance between the processes of resorption and bone production; an aberration in the dynamics of bone repair which in the normal proceeds to restoration but in the afflicted produces dissolution.—*Jack Reynolds, M.D.*

Lindström, Anders. Tomography as an aid in evaluating the results of surgery in epiphysiolysis. *Acta orthop. scandinav.*, 1961, *31*, 316–319. (From: The Orthopaedic Department, University of Gothenburg, Sweden.)

This article demonstrates how tomography can be very helpful in establishing the relationship of the fixation device to the epiphyseal line following open treatment of epiphysiolysis. This is particularly true if routine studies cannot be made.

It is also of value in checking the degree of ossification of the epiphyseal line as healing progresses.—*George L. Sackett, Jr., M.D.*

Blood and Lymph System

Scatliff, James H., Simarak, Sanan, Cutler, Leonard, and Larsen, Parry B. Angiography of the celiac axis: experimental evaluation of methods. *Radiology*, Feb., 1962, *78*, 215–226. (Address: 789 Howard Avenue, New Haven 4, Conn.)

As the scope of radiologic diagnosis expands, the routinely successful visualization of the celiac axis and its branches would appear to be a highly desirable goal. Ödman has emphasized the clinical impor-

tance of this structure by selective catheterization of the artery in an extensive series of patients. His studies not only contributed toward more precise localization of pancreatic tumors but also allowed evaluation of the local extent of gastric carcinoma and the detection of hepatic metastases. In many instances a portogram was produced as the contrast material returned from the spleen.

Therefore, a comprehensive study was initiated to compare various angiographic procedures with selective arterial catheterization. Particular attention was directed toward safety, simplicity, and the production of a maximum amount of information regarding not only the configuration of the major branches of the celiac axis, but also the parenchymal circulation of the pancreas, liver, and stomach. Thirty mongrel dogs were studied using image intensification and cine roentgenography, serial filming, and rotary laminagrams. All injections were by automatic pressure apparatus.

The results of this study represent a well-documented experimental program which has concisely evaluated current or proposed angiographic procedures. These include the selective catheterization of the celiac axis, retrograde aortography with the catheter tip at the level of the celiac axis, retrograde injection during the Valsalva maneuver, EKG-phased injections, balloon occlusion of the aorta with aortography, preliminary use of drugs with aortography, intravenous aortography, and angiolaminagraphy. The best results were obtained by selective catheterization which allowed good demonstration of the celiac axis and its branches as well as a capillary blush of the spleen and liver. Continued filming showed filling of the splenic and portal veins. Retrograde aortography, with the catheter tip at the level of the celiac axis, produced good filling of the artery and its branches but a capillary phase and a portal venous return could not be seen. The other methods were noted to be inferior.

The authors conclude that selective catheterization remains the method of choice at present for thorough visualization of the celiac axis. Retrograde aortic injection at the level of the origin of the celiac artery may be used as a simple and satisfactory alternative for opacification of major branches of the celiac axis. The use of laminagraphy with celiac artery injections of contrast material gives promise of better angiographic definition of the pancreas and gastric wall but this is dependent on future refinement of laminagraphic methods and equipment.—*E. B. Best, M.D.*

Mackenzie, K. G. F., Preston, C. D., Stewart, W., and Haggith, J. H. Thorotrast retention following angiography: case with post-mortem studies. *Clin. Radiol.*, Apr., 1962, *13*, 157–162. (From: The Departments of Surgery, Radiodiagnosis and Pathology, The General Hospital, Shotley Bridge Co., Durham, and the Physics Laboratory, Department of Radiotherapy, Royal Victoria Infirmary, Newcastle upon Tyne, England.)

Although the radioactivity of thorium was well known, it was introduced as a contrast medium in the form of a colloidal suspension of thorium dioxide in 1928. The dangers associated with its use are now recognized, but the late consequences of its retention by the reticulo-endothelial system may appear many years later.

The authors report the case of a man who died 19 years after bilateral femoral arteriography with thorotrast. Roentgenograms revealed opacities in the liver and spleen, originally interpreted as "extensive calcification." At autopsy, chemical examination of liver tissue revealed 200 mg. of thorium per 50 gm. of formalin-treated liver. Histologic sections of liver, spleen, pancreas and lymph nodes along the pancreatic chain showed necrosis of cells, dense overgrowth of fibrous tissue, variable calcium deposition in relation to the thorium deposits and variable thorotrast deposits particularly in the lymph nodes.

The carcinogenic potentiality of thorotrast was discussed by Stewart Einhorn and Illick in 1932, and a recommendation that its use be discontinued was made by these authors and by the American Council of Pharmacy and Chemistry. Several case reports of neoplasm following the use of thorotrast have been given by various authors. However, fibrosis set up in the reticulo-endothelial cells of the liver, spleen and adjacent lymph nodes appears to be of even greater concern because of the frequency of involvement. The progressive cellular damage and reactionary fibrosis produced can, over a long period of years, result in the fatal disorganization of vital abdominal organs.—*Samuel G. Henderson, M.D.*

General

Patterson, J. H., and Watkins, W. L. Leprechaunism in a male infant. *J. Pediat.*, May, 1962, *60*, 730–739. (From: Henrietta Egleston Hospital for Children, Atlanta, Ga.)

The fifth reported case of this syndrome, the first in a male, is presented. The syndrome is a manifestation of a diffuse disturbance of tissues of mesenchymal derivation.

The characteristic features are: anorexia, mental retardation, abnormal facies and ears, breast hypertrophy, masculinization of external genitalia, gonadal hypertrophy, normal androgen excretion, severe malnutrition, muscle wasting, retarded bone age and early death. This patient also demonstrated hirsutism, large nose, dark skin and large hands and feet. The cardiovascular and gastrointestinal systems and urinary tracts were normal. No family history of similar abnormalities was elicited.

The long bone surveys, not described with previous

cases, revealed a diffuse, generalized, progressive rarefaction of the entire skeleton. There was marked irregularity of the metaphyses and epiphyses. The bone age was retarded. All the changes progressed over the 9 month period of observation. The dental development was normal at 6 months.

The endocrine studies were normal other than decreased compensatory response to hypoglycemia. Low serum and connective tissue phosphate activity was present but a diagnosis of hypophosphatasia was not considered valid.—*Barry Gerald, M.D.*

BUCHET, R., and LEBLANC, J. (Paris, France.) Maladie polykystique du foie et des reins: à propos de deux cas; aspect radiologique du problème. (Polycystic disease of the liver and kidneys: contribution of two case reports; radiologic aspect of the problem.) *J. de radiol., d'électrol. et de méd. nucléaire*, Jan.–Feb., 1962, *43*, 12–20.

Among cystic visceral dystrophies polycystic disease of the liver is rare as evidenced by the limited number of cases reported in the literature. The cysts develop from or at the expense of the normal or newly formed biliary ducts. True hepatic cells are not involved. From the anatomic point of view one may distinguish between polycystic disease of the liver, solitary cysts of nonparasitic origin and congenital hepatic fibrosis. The condition is four times more prevalent in female than male subjects.

Clinically, there is a very large, usually silent liver which constitutes the basic sign or symptom of the disease. The enlargement is painless and nodular. There is no accompanying ascites or jaundice. Blood chemistry studies are normal. Occasionally, there may be associated pain in the right upper quadrant, symptoms of compression of the liver hilus, rupture or torsion.

Rare as polycystic disease of the liver is, the association of polycystic disease of the liver and of the kidney is not infrequent. Reported incidences vary between 40 and 60 per cent. Those patients who have concomitant polycystic renal disease usually die between the ages of 40 and 50, due to renal insufficiency. Furthermore, the discovery of polycystic disease of the kidney should lead to the diagnosis of the same condition in the liver when concomitant hepatomegaly is present.

The roentgen studies include: plain film of the abdomen, which reveals enlargement of the liver; contrast studies of the biliary tract by means of oral and/or intravenous cholecystocholangiography for demonstration of compression and displacement of the gallbladder and major bile ducts; liver scanning following the use of radioactive gold or rose bengal to show multiple defects indicating the size and location of the cysts. Subhepatic phlebography may give additional information.

Studies of the urinary tract by intravenous urography will reveal changes due to multiple cysts of the kidneys when present.

In the case of portal hypertension esophageal studies disclose the presence of varices. After successful surgery with clearing of the portal hypertension the varices disappear.—*William H. Shehadi, M.D.*

RADIATION THERAPY

FEDER, BERNARD H., and SMITH, JOHN L. Roentgen therapy in chronic spinal arachnoiditis. *Radiology*, Feb., 1962, *78*, 192–198. (From: Long Beach VA Hospital, Long Beach, Calif.)

The authors call attention to the possible beneficial effects of roentgen therapy in chronic arachnoiditis and report the results in a series of 17 treated cases. Most of the cases were diagnosed either by myelography or at laminectomy, and none were considered amenable to surgery.

Chronic arachnoiditis may be localized or disseminated but usually is confined either to the brain or the cord. The primary finding in arachnoiditis is a diffuse, pearly white thickening of the leptomeninges. The spinal roots may be compressed and show definite demyelinization, destruction of nerve fibers and even replacement of nerve fibers by fibrous tissue. The cord is rarely involved. Microscopically there is a diffuse but patchy thickening of the leptomeninges.

Usually there is a history of back trauma, followed by an asymptomatic period of months or years. The presenting symptom is a burning type of pain occurring over one or more spinal segments and influenced by motion, cough, etc. Hyperesthesia or paresthesia in the distributions of the involved segments is common. When present, typical myelographic findings are of great aid in diagnosis. Arachnoid block without xanthochromia or increased spinal protein is suggestive of the condition. A diagnosis is often impossible without laminectomy.

Surgical approach by laminectomy is the procedure of choice in almost all cases of spinal arachnoiditis. If localized arachnoiditis is found, surgical lysis of constricting lesions will often give immediate and dramatic relief. If disseminated arachnoiditis is found, the chances of surgical success are meager, and roentgen therapy should be considered.

The authors irradiated the area of cord involvement with relatively small doses through generous posterior ports, repeating the course of treatment as indicated. Generally, 1 to 3 courses of treatment were given at intervals of 3 months to 3 years. A course consisted of 600 to 800 r (air) delivered in increments of 100 to 200 r (air) daily, the ports being treated in rotation. The port size varied from 8×10 cm. to 10×20 cm. The physical factors were 250 kv., 0.5 mm. Cu filtration, 1.7 mm. Cu half-value layer, 50 cm. target skin distance. After completion

of the initial course of treatment the patient was re-evaluated. If there was no improvement or if progression of disease had occurred, the treatment course was repeated within an interval of not less than 3 months.

No serious complications were observed in the 1 to 7 year period following therapy. Four patients manifested excellent clinical response following treatment, with return of motor and sensory function; 4 patients improved to a limited degree with only partial control of symptoms; in 5 there was an apparent arrest of the disease that had been progressing prior to therapy; the remaining 4 patients showed no response and no arrest of progression.

The response is attributed to the inhibitory action of small doses of irradiation on connective tissue proliferation.

It is concluded that radiation therapy is justified in chronic adhesive spinal arachnoiditis not amenable to surgical alleviation.—*A. W. Sommer, M.D.*

Falchi, Q., and Valpreda, G. Manifestazioni bronchopolmonari acute in corso di trattamenti radioterapici con particolare riguardo alla telecobaltoterapia. (Acute bronchopulmonary manifestations during radiotherapy, with particular consideration of telecobalt therapy.) *Radiol med.*, Jan., 1962, *48*, 37–51. (From: Istituto di Radiologia dell 'Università di Genova, Genova, Italy.)

The authors note the greater incidence of acute pulmonary lesions following traditional roentgen therapy with fixed beam when compared with telecobalt therapy.

The percentage of acute bronchopulmonary complications during the course of telecobalt therapy in 145 cases studied was 3.45 per cent. It compares more than favorably with the 22 per cent quoted by other authors, as occurring during orthovoltage therapy.

This series of cases includes, principally, treatment of neoplastic lesions of the esophagus, of the breast, and of the lungs.— *Anthony A. Blasi, M.D.*

Nelson, D. H. Spontaneous regression of cancer. *Clin. Radiol.*, Apr., 1962, *13*, 138–140. (From: X-ray Department, Royal Victoria Hospital, Folkestone, Kent, in conjunction with the South Metropolitan Cancer Registry.)

In this article 5 case reports are given, each describing spontaneous regression of a neoplasm.

The criteria for inclusion under this category are (a) histologic proof with independent confirmation by three experienced pathologists, (b) no treatment or palliation only, and (c) survival for more than 5 years with no clinical signs of activity, or no trace of the original disease on subsequent surgery or post-mortem examination.

The author states that cancer may regress in five ways: (1) Spontaneous disappearance of tumors, primary or secondary; (2) disappearance of secondary lesions after removal of the primary growth; (3) temporary regression of primary or secondary lesions, and later re-activation; (4) regression of some secondary lesions and continued growth of other lesions in the same patient, with or without treatment of the primary tumor; and (5) long interval of 10 years or more after removal of the primary lesion before evidence of metastases becomes apparent.

These various possibilities suggest that cancer can be a reversible condition under special circumstances, with hormone dependency as one likely factor.—*Samuel G. Henderson, M.D.*

RADIOISOTOPES

Dawson, John W., and Duffin, John D. Radioiodine studies in euthyroid subject following cessation of propylthiouracil administration. *Canad. M.A.J.*, Apr., 1962, *86*, 698–699. (From: The Departments of Medicine and Laboratories, Colonel Belcher Hospital, D. V. A., Calgary, Alberta, Canada.)

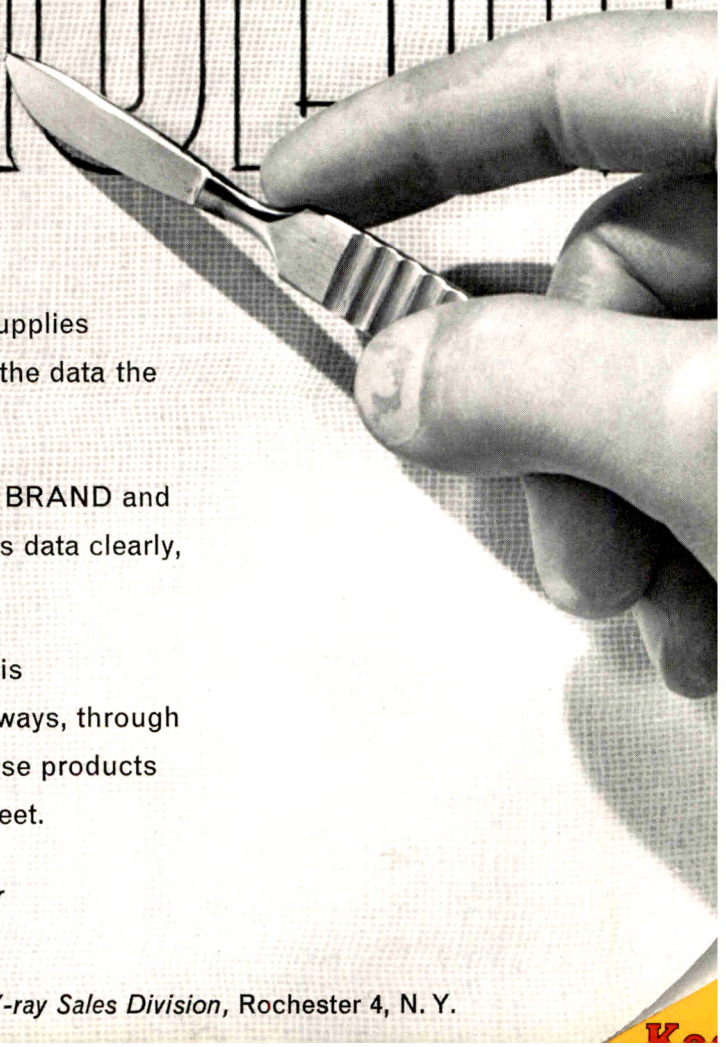
The authors report their findings in 14 cases of euthyroid subjects treated with propylthiouracil in evaluation of the rebound phenomenon.

They selected male patients over 45 who had been in the hospital one year; thus, medications and previous studies were known. Each patient was examined and determined to be euthyroid with no significant debilitating disease. After study with 40 μc of I^{131} similar determinations were made on those taken for baseline.

Their results showed no change in 8 cases; a mild upward trend in 4; and 2 cases exhibited significant increase in both the uptake and conversion ratio levels. However, all values were considered within normal limits.

In the authors' opinion, it would appear that in the euthyroid person, in contradistinction to the hyperthyroid, a rebound phenomenon following the withdrawal of propylthiouracil is likely to be, at most, transitory and short-lived.—*George A. Kling, M.D.*

BEFORE SURGERY



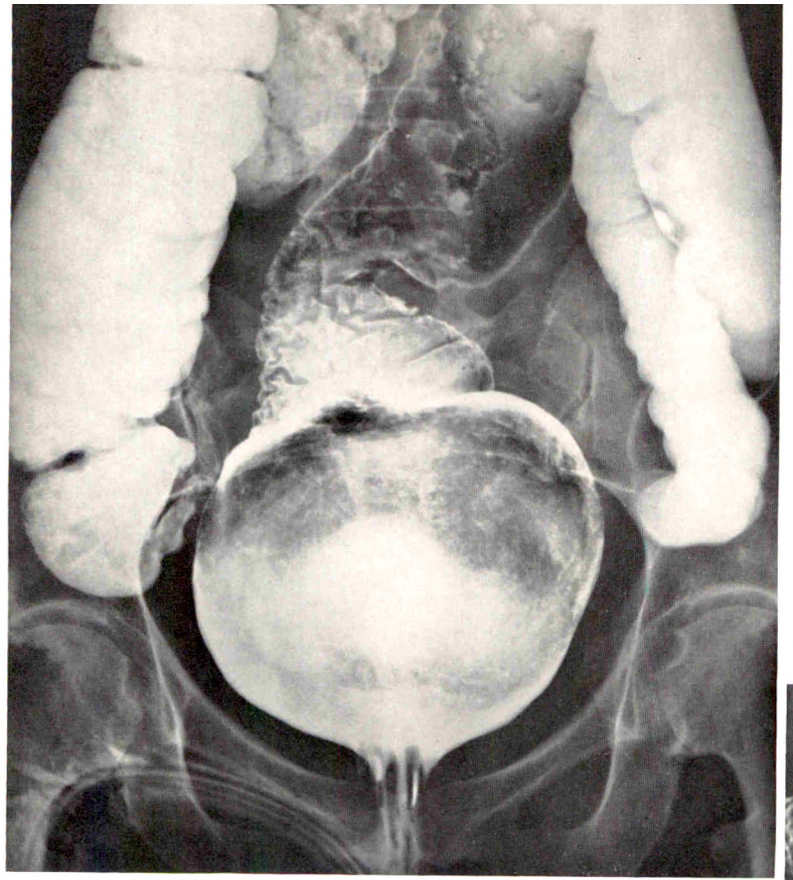
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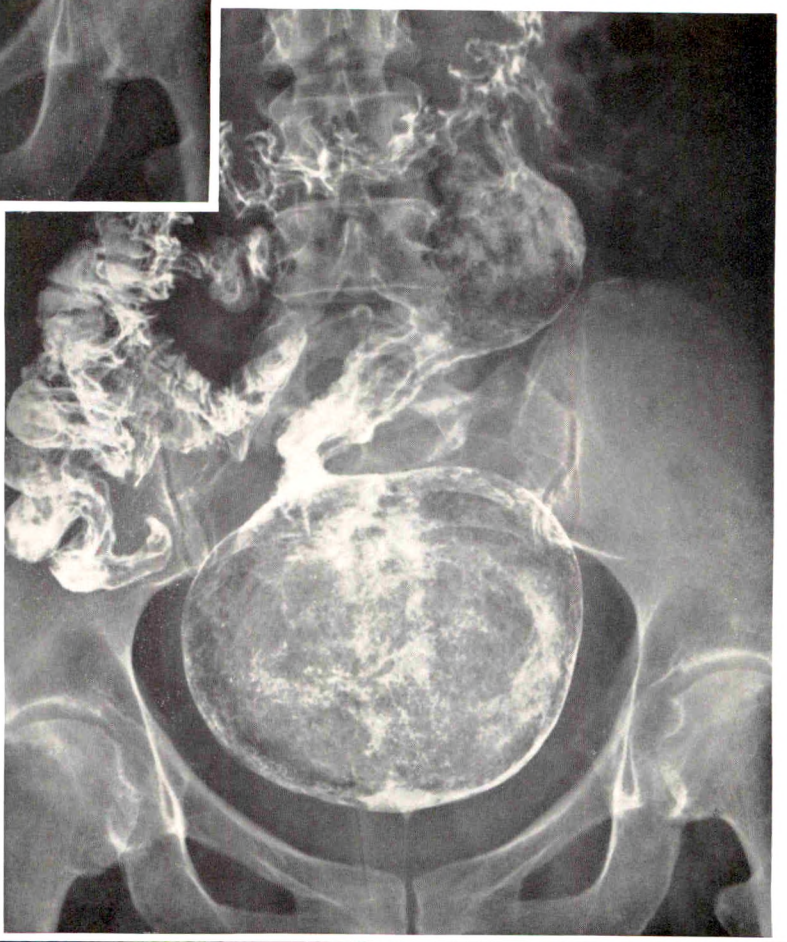
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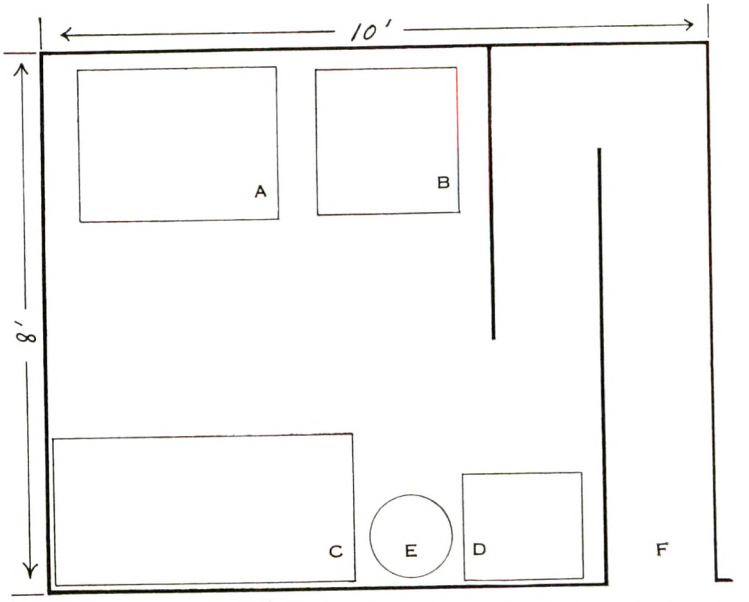
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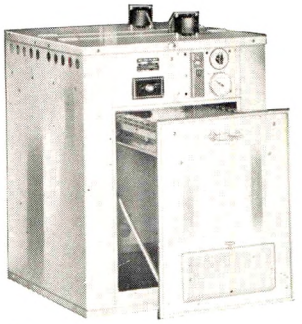


A--FL. SP., 26 X 36 IN.

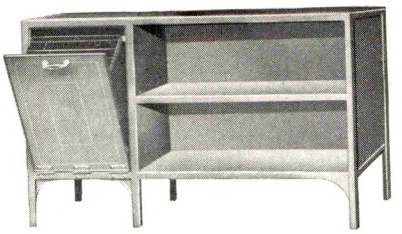


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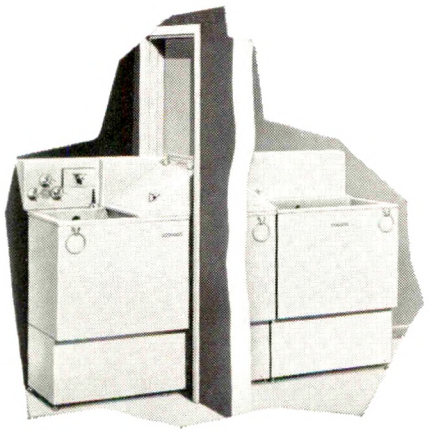
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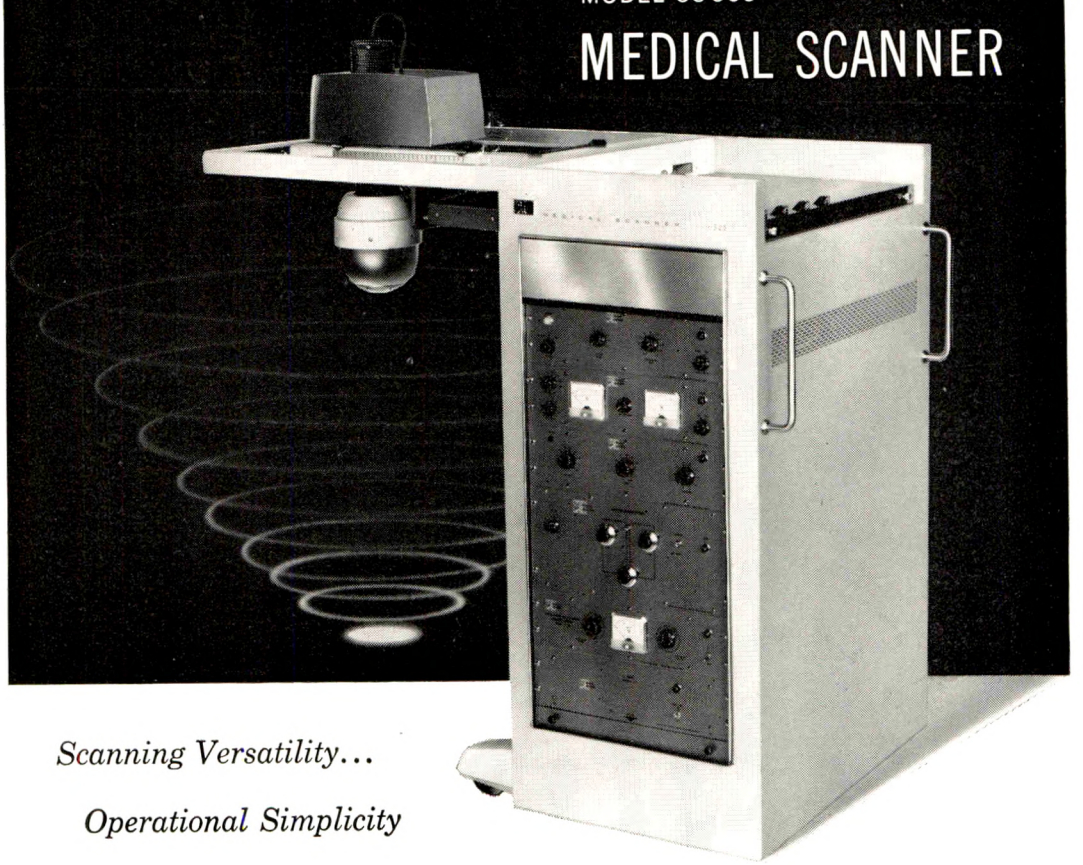
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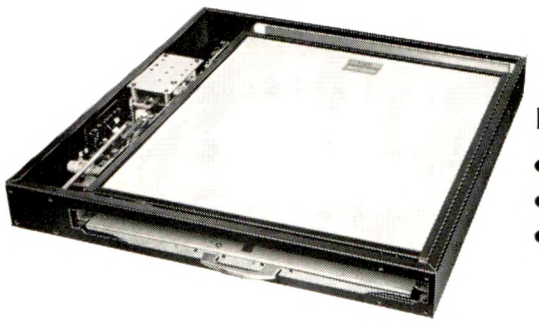
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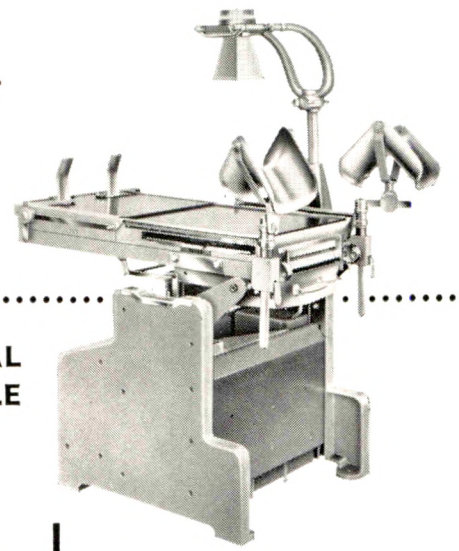


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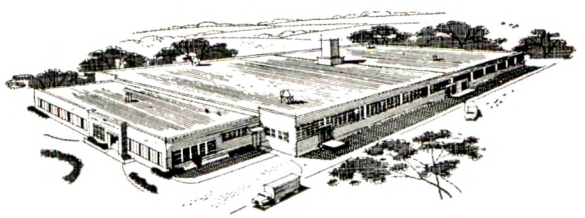
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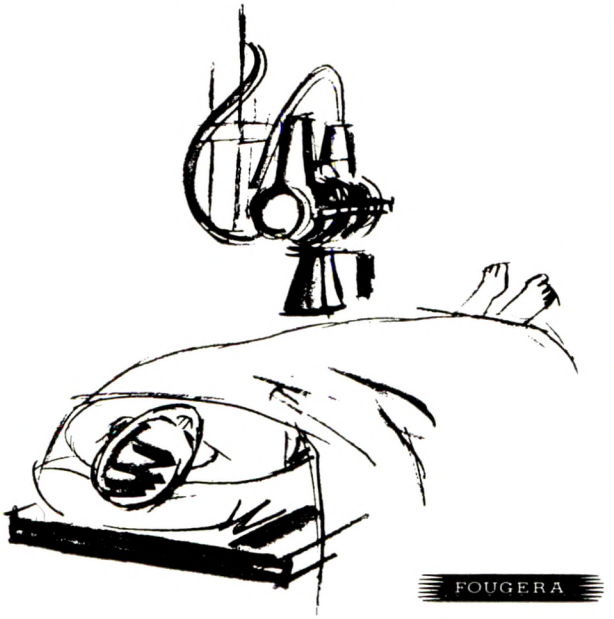
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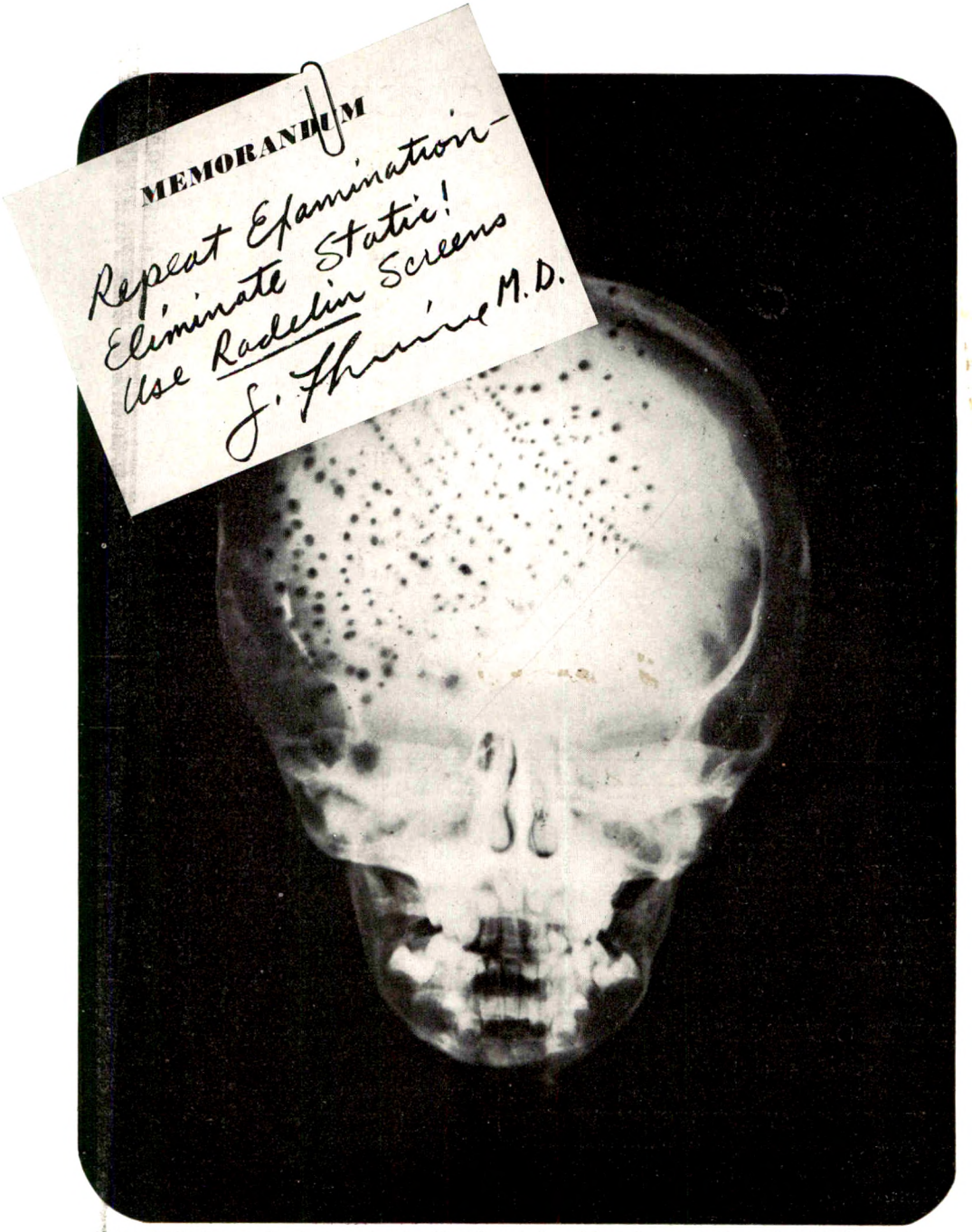
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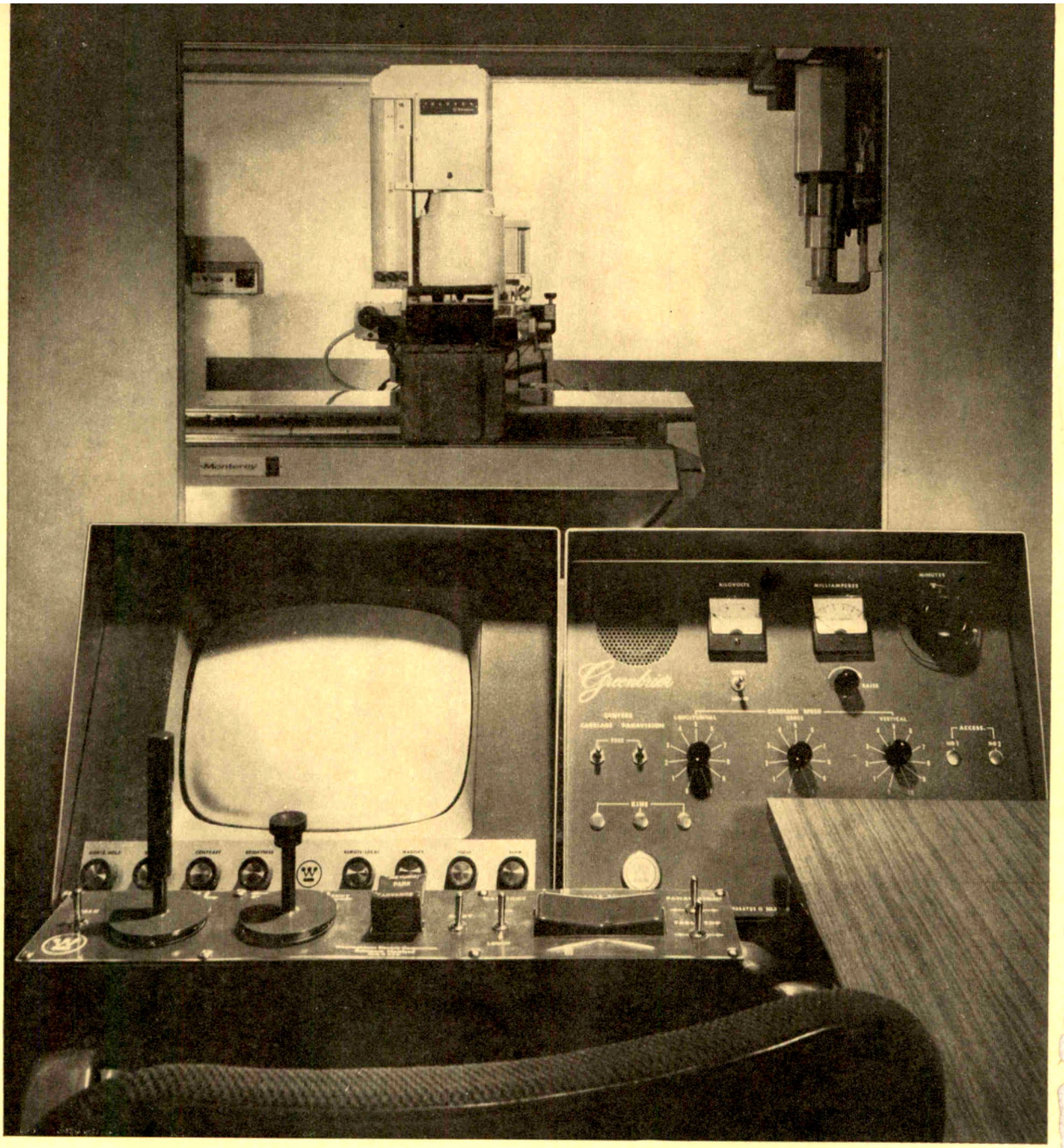
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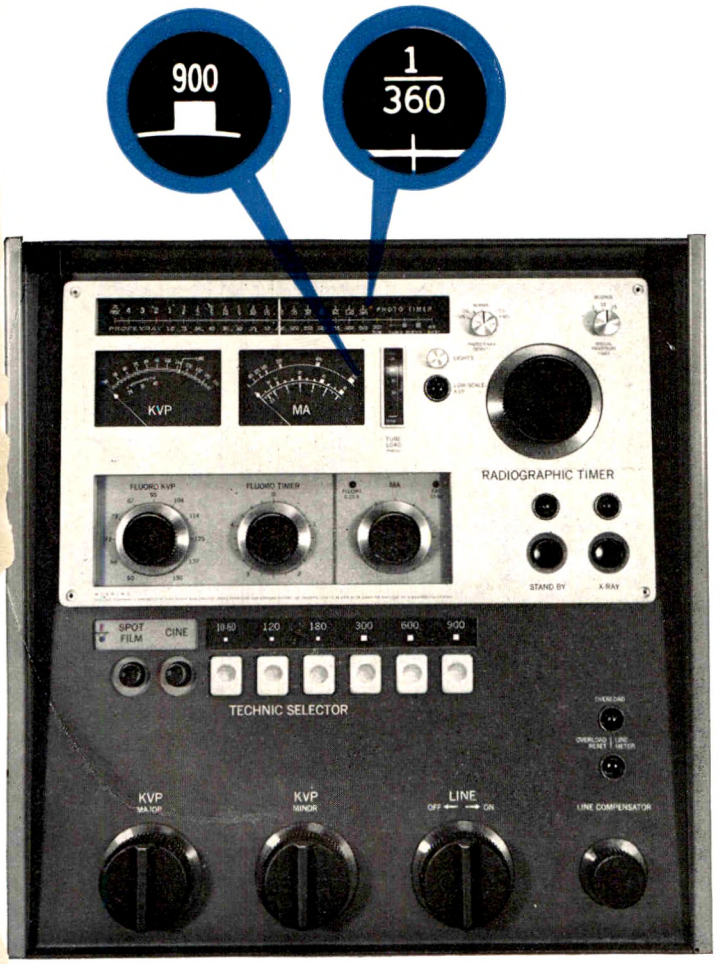
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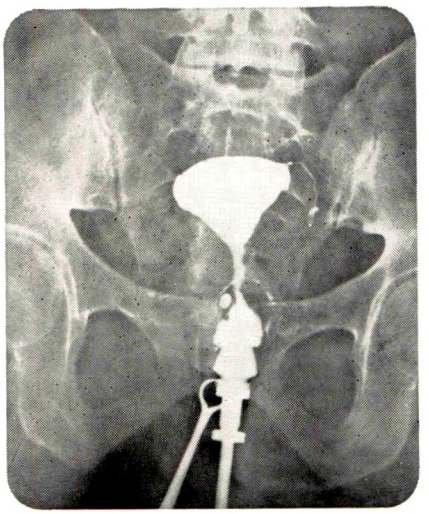
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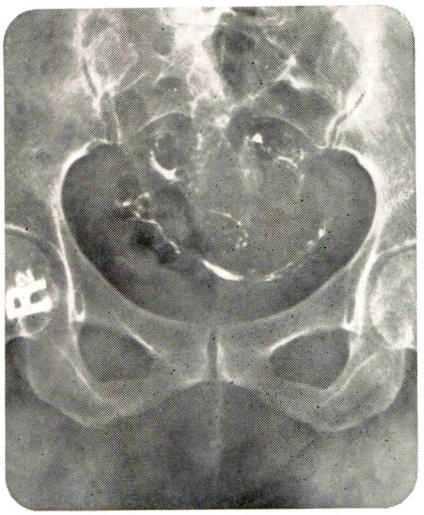
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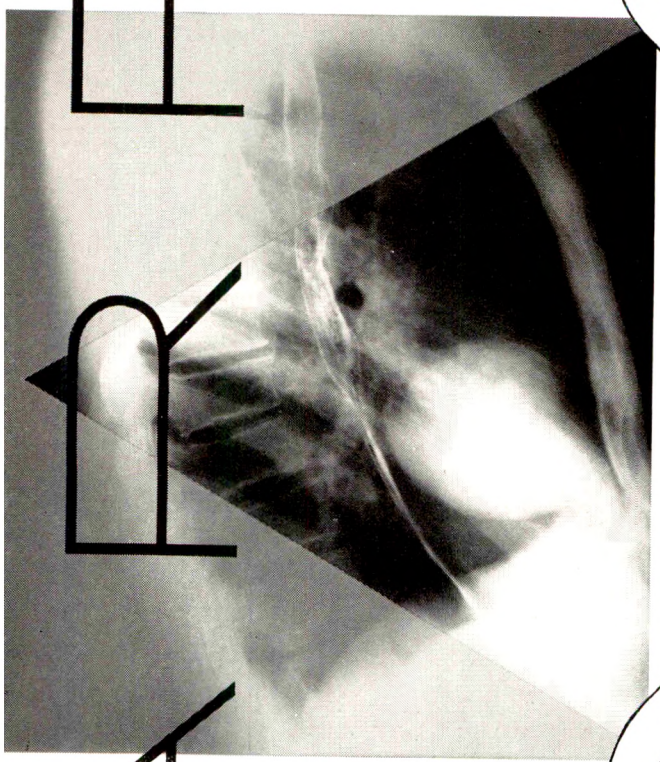
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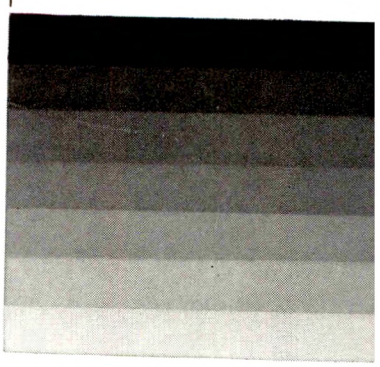
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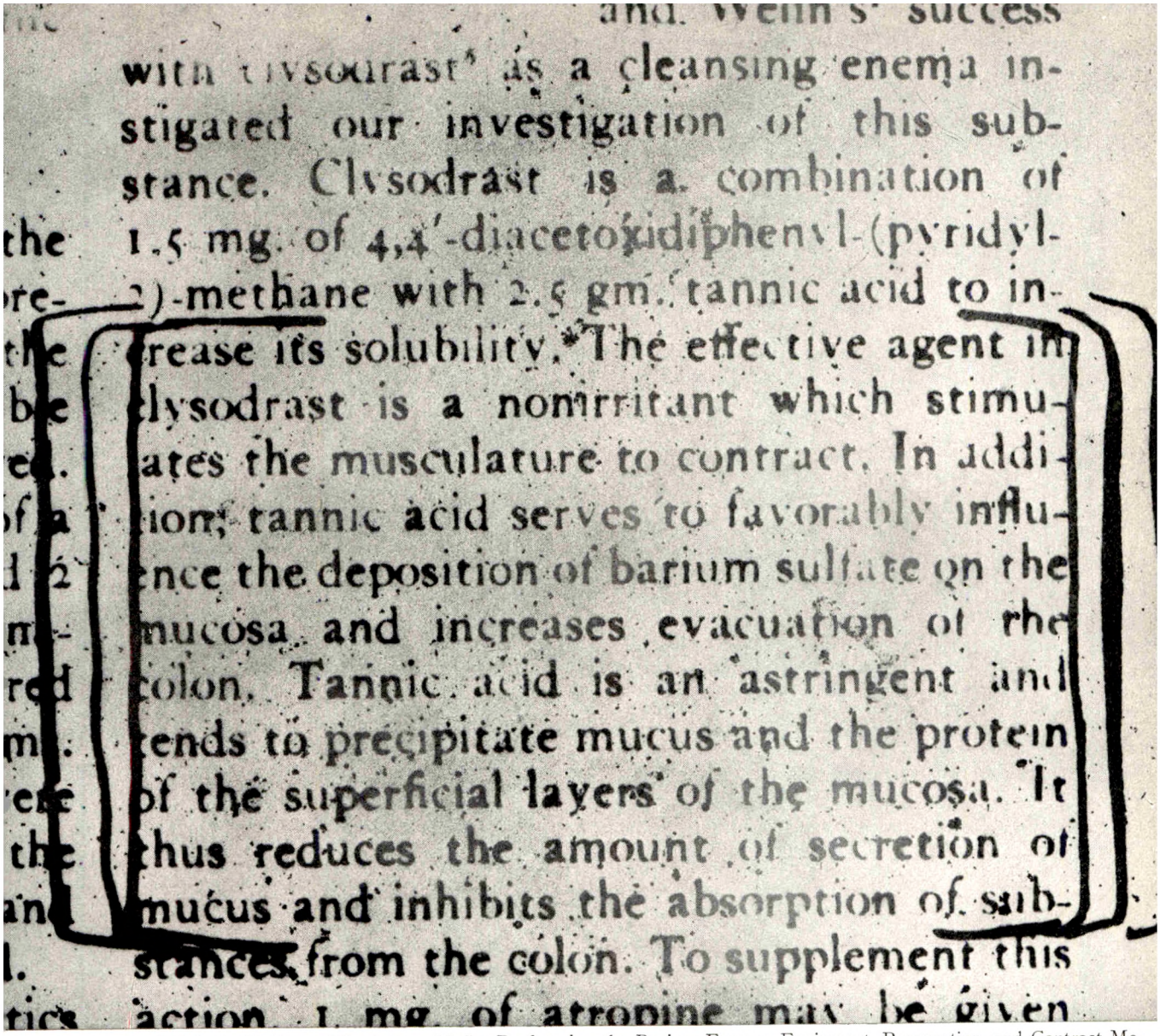
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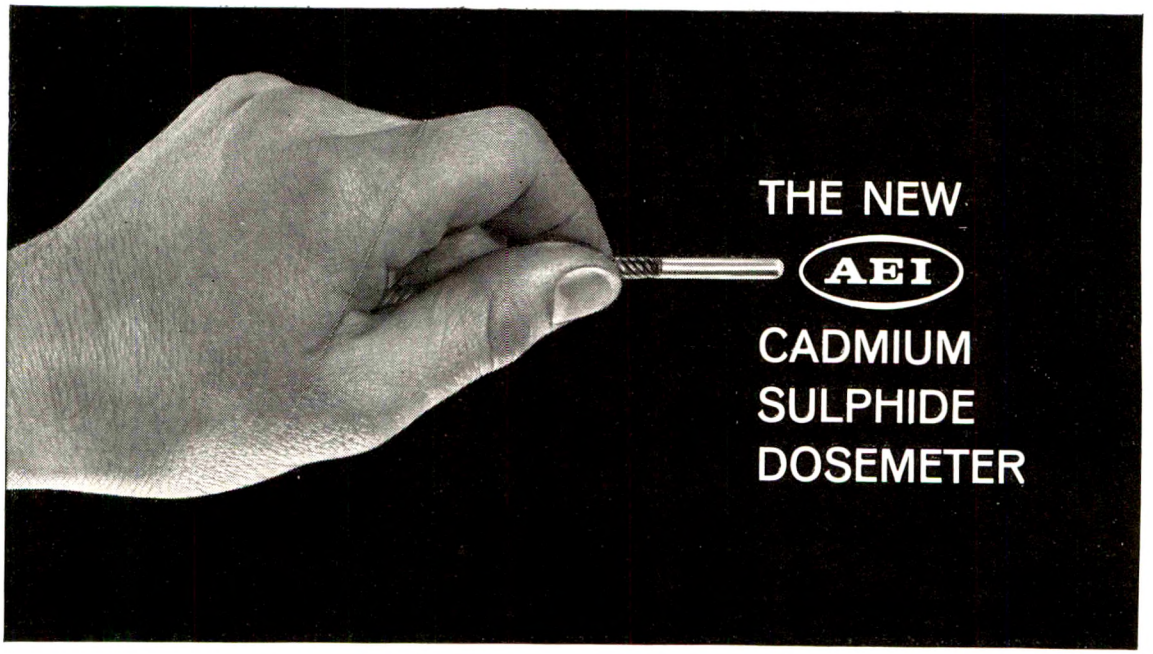
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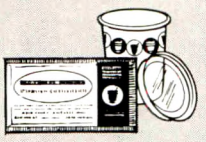
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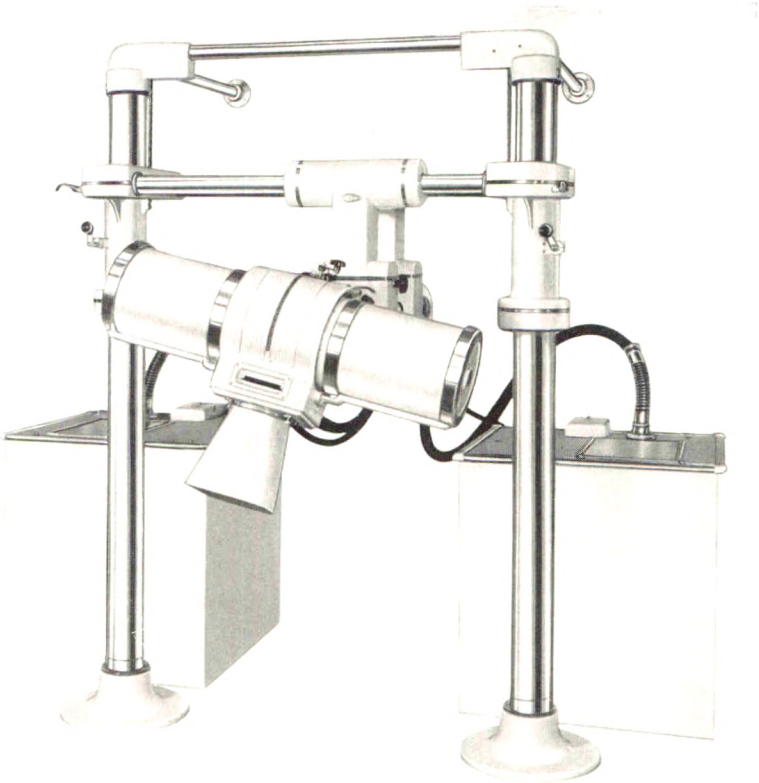
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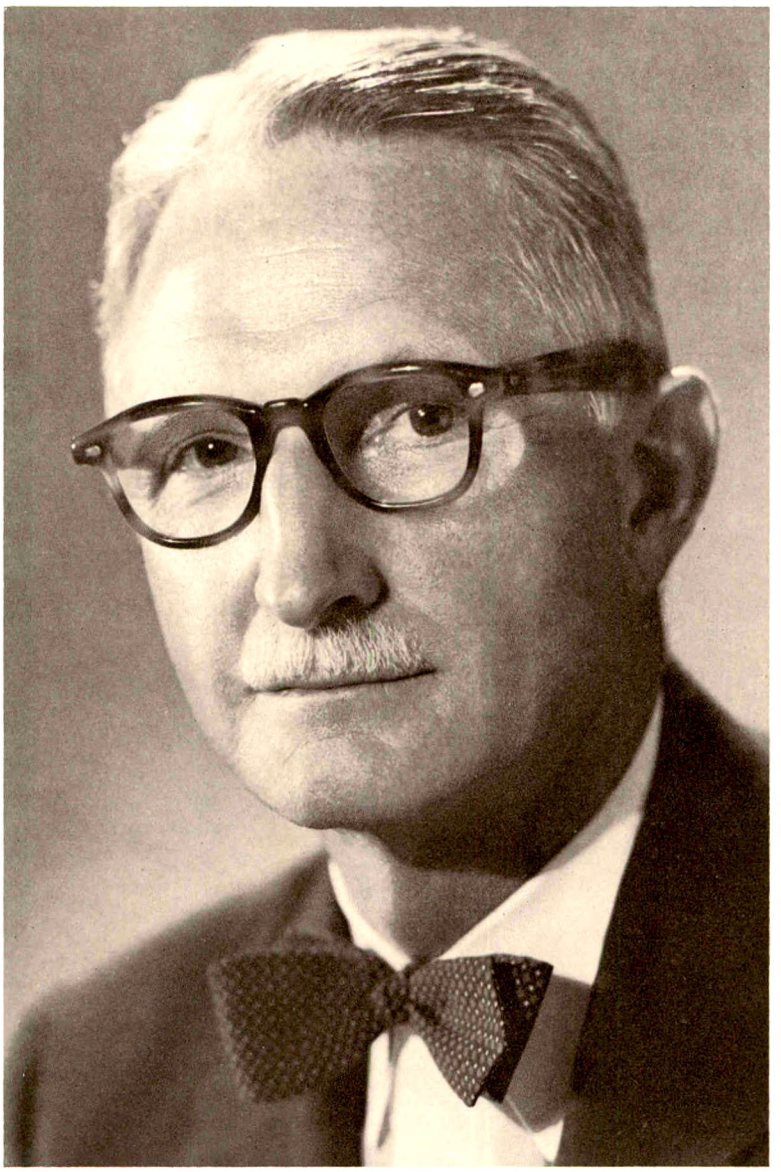
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EARL E. BARTH, M.D.

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RADIOLOGY AND THE CHANGING MEDICAL SCENE*

THE PRESIDENT'S ADDRESS

By EARL E. BARTH, M.D.
CHICAGO, ILLINOIS

IT IS with a sense of combined humility and pride that I assume the presidency of the American Roentgen Ray Society at this the Sixty-third Annual Meeting. To be elected President of the oldest radiological organization in America and the second oldest in the world is one of the greatest honors that can be bestowed upon a radiologist. I am profoundly grateful to you, fellow members, for this honor. It is my ardent hope that I may prove worthy of the confidence you, my friends, have placed in me. My feelings are perhaps best expressed by the words of MacNiele Dixon in introducing his Gifford Lectures, and which were also used by Past-President H. Dabney Kerr in his presidential address to this Society in 1951:

"If it be said, and it is no more than truth to say, that I owe my position here to the friendship of my colleagues, I wish this to be added that I take more pleasure in the regard of my friends than in any honor that could be done me."

It has been my rare good fortune over the past years to be entrusted by my colleagues with a series of responsibilities for the well being of our specialty. I hope that I have been worthy of this trust—I know that I have been enriched and made a better man by holding it. As I sat in the deliberations of the American College of Radiology, the American Board of Radiology, the Residency Review Committee and our own pioneer society, I have been proud of the accomplishments of radiology.

Ours is truly a modern specialty, born in the discovery of x-ray and radium, which has contributed so much to medicine. I have no fear that we shall make even greater contributions in the future.

But these are changing times. Winds of change are blowing from many directions and could change our way of life in radiology. The political, cultural, social and economic upheavals of today are affecting every level of human behavior. Oliver Wendell Holmes has said, "The truth is, that medicine, professedly founded on observation, is as sensitive to outside influ-

* From the Department of Radiology, Northwestern University Medical School and Passavant Memorial Hospital, Chicago, Illinois. Presented at the Sixty-third Annual Meeting of the American Roentgen Ray Society, Washington, D. C., October 2–5, 1962.

ences—political, religious, philosophical, imaginative—as is the barometer to the change of atmospheric density." It becomes apparent that these changes will affect radiology. This is our challenge.

As a member of the American Board of Radiology, I have been particularly conscious of the responsibility of radiology to recruit and train bright young men and women to take up our burden for future generations. To do this, we must help to bring talented young people into medicine, where the need for them is great. Then we must attract the best of these physicians into radiology. The future of radiology will rest in their hands. This is no light or simple task. It is complicated by many factors which I would like to consider under the theme of "Radiology and the Changing Medical Scene."

I have noted recently that I am less frequently challenged to explain radiology. Instead, I find myself involved in a discussion or debate about medical economics—the cost of medical care. I am particularly grieved in these discussions to find what I might call an attitude of skepticism about the doctor's motive in the practice of medicine.

You will understand that few of these skeptics are aware of the complexity of modern scientific medicine. They do not understand how physician skills, equipment and facilities are provided—or paid for. They do not understand the composition of the basic costs of medical care. Their only interest is the end product—good care for themselves. If the manner of paying for medical care affects the quality of medicine we practice, then we must explain how certain changes would be harmful. Those who preach change seldom trouble themselves to explain all that could be changed and lost under another method of payment.

Too frequently we have not bothered to explain these things. There have been efforts. The College's insurance education program is a continuing example of an excellent one. But mostly, they have been too little and too late. And, if it is not too late, we can only blame ourselves if it is too little.

When we pause to think, we all recognize that our usual and ordinary practices in medicine today are based on an explosion in medical knowledge that has occurred since many of us graduated from medical school. Through scientific advances, to which the members of this society have greatly contributed, radiologists are far better able to serve their patients than ever before. But radiological service is a complex and ever increasingly expensive business. Few quarrel with the quality of medical care, but many stumble endlessly over the ways and means of providing for this care.

Since radiology will undoubtedly be affected by these changes in the medical scene, let us touch on several points which I believe to be challenges to us now and in the future.

The first is the role of government—particularly federal government—in medicine. This has increased enormously in all aspects of medicine. I would not dispute that government support for research, hospital construction and teaching has not been beneficial, but I do believe that we still have a fundamental responsibility in these programs. Further, the basic provisions of professional services should remain with the physician, outside of government control.

It has been said that government has the obligation to do for people what they cannot do otherwise. We hold that the provision of radiological care can be accomplished otherwise. But this is not enough. We must do everything possible to prevent the control of our radiological practice by others. We must work with our patients and with their "third parties." We need allies from outside our own ranks.

A second change in the medical scene is the rise in what has been called institutionalized medicine. In this is included group practice of medicine, clinics, hospitals, medical buildings constructed and owned by hospitals and community health centers. Certainly, radiology is involved in this

change. Our tools are complex and expensive. Our services are needed for all ranges of patients, including those hospitalized for total care. In the field of therapy, the grouping of skills and equipment in centers is a reasonable and economical way of providing these services. In radiology we work with a team of others, and we integrate our contribution with the over-all care of the patient. This integration of disciplines is desirable, but not in the context which makes a physician subservient to the structure, and makes the care he renders dependent upon any other factor than his medical judgment. Radiology is the practice of medicine. Radiologists should have all the rights and privileges of their colleagues in other disciplines. There should be no discrimination.

These changes have had an impact on the private practice of radiology which is beset by a variety of serious threats. With the increasing practice of radiology in hospitals, with the increasing inclusion of radiology as an insured benefit only if provided in a hospital department, with the construction of hospital-owned office buildings or provisions for office space within the hospital, the outpatient services have grown disproportionately. Private office radiology has suffered. It is in the interest of the profession and the public that competent radiologic service be readily available. The private and/or office practice of radiology is a significant factor in making such services available. Radiology must never be so "scientific" and so involved in technical features, nor so institutionalized, that the patient ceases to be the main concern. The public welfare is the only reason for our existence.

We all know and have said many times that most radiology except for special procedures can be done as well in a private office as in a hospital department. If a patient needs hospitalization for medical reasons, then, certainly, radiology should be provided in the hospital. If the patient has no medical indication for bed care, it seems unreasonable to use needed bed space and to incur unnecessary expense by placing him in the hospital for radiological services. It is similarly unreasonable to prefer hospital outpatient service to private office care. The cost is seldom less, the incidence of use is not diminished, and the inequity is only prolonged.

It may be that the role of government in medicine is basically irreversible in its trend. It is certain that centralization of facilities, of talent and of service is a positive good. But it is likewise certain that extremes of federalization and institutionalization are destructive of their own ends. Private offices, where a radiologist is judged by his own service, responsible to his own professional standards and the good opinion of his colleagues, can be a most efficient and rewarding way of practicing radiology. I would, indeed, be distressed to see the demise of the private practice of radiology, which certainly would serve to make our specialty less attractive to young men and women.

There is another matter of some concern to all radiologists in all phases of practice. It is tied together with the so-called institutionalization, the wane of private practice and the general trend of change. I refer to the splintering of radiology into other types of practice. Radiologists have been remiss in their obligation to the specialty as other physicians reached out to take over more and more of what should be the proper domain of the radiologist. This is harmful because it affects the future of radiology. It is wrong because the trend encourages unqualified and untrained persons to think themselves capable of performing certain radiologic procedures and often without knowledge of the hazards of irradiation—a dangerous misapprehension for physician and patient.

There never has been a time in the history of radiology when its practitioners wished to limit totally the medical uses of x-ray to their own members. But let us recognize that in this time of radiation safety consciousness and this era of medical specialization, it behooves us to be sharply

aware of this problem. The proper exposure and interpretation of a roentgenogram is not a casual art. We have gained our competence through rigorous training and long experience. Likewise, the use of radiation for therapy and the handling of radioactive materials are not procedures to be attempted on an occasional basis.

If we expect our specialty to be attractive to young physicians, it must have a place in medicine, recognized by all, with its proper role to play in diagnosis and therapy. Radiology must not be allowed to become a sort of interstitial area between the specialists in other disciplines who have some uses for radiologic procedures in their own practice. If we are to be responsible for the use of x-ray and radioactive materials in medicine, then we must make every effort to discourage these uses by the untrained and unqualified. Responsibility without control and without authority is not good; it is particularly not good for the specialty of radiology.

This brings me to another challenging point in this inaugural address. The decline in the prestige of the doctor is a subject of almost endless discussion these days. But, to me, the evidence submitted to prove this decline or that we have forfeited the basic respect of our patients is not persuasive. That people question us now is more a reflection of their higher education and understanding of medicine than of any fundamental shortcoming in medical care. The fact is that today's patient, on the average, is vastly more sophisticated medically than his counterpart 20 or 30 years ago. Assuredly, none of us occupy the renowned pedestal of the old family doctor. But, due to the advancements in our science, we are more capable physicians than he was—and none of our critics would dispute this. We may witness violent disagreement over health financing for the aged, but there is no proposition that anyone else could provide the service or that the care we give is insufficient. These disputes over ways and means have not shattered the basic confidence of our patients in our medical wisdom.

It is suggested that we recognize this basic strength and build upon it. The image people hold of a doctor is based upon their own experience with their own doctor and the physicians to whom they are referred. If we would have patients think well of the radiologist, we must give them cause to do so. Since radiology is the practice of medicine, we must conduct ourselves in such a manner that the patient will fully realize that the radiological medical service is being rendered by a radiologist who is foremost a physician. Our entire staff should be oriented in this direction. Radiology should be—must be—people oriented.

A considerable part of our organized efforts should be devoted to telling the story of radiology through every public means of communication available. But the basic way to tell the story is through our own actions. There can be no substitute for service in radiology. The public is eager for such individual care.

The last of the cardinal problems I wish to discuss is the whole matter of communications. Like the others cited, it is a problem which is interwoven with the whole milieu of modern medicine and modern society. The very ease of communication today may well be self-defeating. In the same way that radiology has grown with technology, so has communication. We have not only the mail to carry letters but to spill out a never-ending mountain of printed materials across our desks each day. With radio and television and their medical uses, the physician has access to much more than he can ever hope to learn, understand or remember. The very task of selecting out of this stream those portions of primary concern is a demanding one.

Frequently, during my service in radiology, letters have been received from colleagues in which they asked questions about organizational policy, or took violent exception to some policy which they had obviously failed to understand. Yet, I could

refer them to letters, pamphlets, bulletins, articles in the scientific journals, talks at various meetings and other efforts to inform them. "I didn't see that," or "I didn't hear that paper" was the most frequent response when I had pointed out the availability of the requested information. Never in the history of radiology has there been a greater need for good interprofessional and interdisciplinary relations and good liaison. This will depend in large part on good communication.

It is a trite, but true, saying that one may receive from an organization exactly that which he puts into it, and no amount of writing or talking will do the job unless there is complete and universal participation.

Based on my experience, a precept has been formulated which I would call the radiologist's duty to be informed. Radiological organizations and medical organizations are not basically remiss in their communication efforts. Most of the materials we receive are prepared well. They contain a message expressed clearly and usually with considerable appreciation for the recipient's need for the information.

It has been stated that the problem in communicating with the patient would be taking time to talk. Now it should be stated that the problem in communicating with colleagues lies in taking the time to listen or to read—and to understand.

In this inaugural address, all that has been stated rests upon experience gained in attempting to discharge the responsibilities that have been assigned to me in our specialty. These reflections represent one man's effort to present the challenges that confront Medicine, and, in particular, Radiology in the changing medical scene. The future of our specialty will depend on how we meet these challenges. It should be emphasized that Radiology has many strengths. It has attracted good people to its ranks. They have been trained well and serve well. But, to continue to provide the nation with good radiologic care, an adequate number of good radiologists is absolutely essential. Every effort should be made to produce such a radiologic climate that good young men and women will be attracted to our specialty.

If we are able to maintain radiology in this mold, we must devote ourselves to insuring that the residents who come to us are trained as whole radiologists. We must see that they understand not only the science of radiology but also the art of practice. They must be oriented in the nonscientific phases of the practice of radiology. Let us never forget that the future of our specialty is in their hands. The only certain way to guarantee this future is to conduct ourselves so as to reflect our own understanding and exemplification of our ideals and our objectives.

As I assume the responsibilities of the presidency, my mind is troubled, but I am full of hope. Radiology has given much and has much to give. The healing professions are among man's highest callings. Radiology is a vital part of the healing art, and our good true service is essential to the advance of medicine.

You have honored me greatly in calling me to this position. With the help of all who have put me here, I pledge my own best efforts towards the advancement of Radiology and of this Society.

670 No. Michigan Avenue
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THE SOLITARY NODULE (COIN LESION) OF THE LUNG*

AN ANALYSIS OF 52 CONSECUTIVE CASES TREATED BY THORACOTOMY AND A STUDY OF PREOPERATIVE DIAGNOSTIC ACCURACY

By WALTON M. EDWARDS, COL., MC,† ROBERT S. COX, JR., MAJOR, MC,‡ *and* L. HENRY GARLAND, M.B., M.D.§
SAN FRANCISCO, CALIFORNIA

OVER 20 years ago Graham and Singer[7] reported 3 cases of resected calcified pulmonary lesions due to tuberculosis which were removed because of the possibility of malignancy. In the present era, some physicians feel that small ovoid lesions of the lung can be diagnosed only by surgical excision and that the frequency of malignancy makes conservative management dangerous. "Time consuming" diagnostic studies are not felt to be helpful, and early thoracotomy and excision are believed to be the treatment of choice.[2,5,15]

The term "coin lesion" of the lung has varied meanings. The definition is not precise and the different composition of cases in series reported accounts for the variation in the incidence of malignancy, ranging from 2.2 per cent to 78.3 per cent.[8] French *et al.*,[5] reviewing the English literature and contributing 36 cases (included in this series), found an incidence of malignancy of 11.1 per cent in their own series and 34 per cent in the 356 cases reviewed. These authors considered any rounded density under 5 cm. in diameter to represent a coin lesion.

Higginson discussing the presentation of French *et al.*,[5] and referring to their own previously reported series, emphasized the importance of the term "coin lesion" and listed 9 criteria for the selection of patients. Davis *et al.*[3] reviewed all personally resected noncalcified pulmonary lesions and found an incidence of malignancy of 57 per cent. They concluded that every solitary noncalcified pulmonary nodule required a thoracotomy. The size of the lesions reported in various series was not specified except by Sharp and Kinsella,[19] Storey *et al.*,[20] Gregory and Harris,[8] Higginson and Hinshaw,[9] and Davis *et al.*[3] Gregory and Harris[8] listed the following simple criteria for "coin lesions": (1) 1 to 4 cm. in diameter; (2) rounded to ovoid with sharp, circumscribed borders; (3) surrounded by normal appearing lung on all sides; and (4) homogeneous density or containing calcium. Other authors (cited in Reference 9) have included the following additional criteria: (5) the lesion is solitary; (6) the patient is asymptomatic; and (7) the histologic diagnosis has not been established by bronchoscopic examination. Finally, some would include a broader spectrum of size—for example, from 0.5 to 7 cm. in diameter.

A point of contention centers on just what is considered as a round or ovoid lesion with sharp, circumscribed borders. Questions regarding size, surrounding tissue, and density are usually readily agreed upon. Rigler and Heitzman[18] directed attention to a sign which they believed suggestive of a malignant nodule, a notching of the border of the density of variable depth, best seen on laminagrams.

* This project was carried out under Project 6-60-01-002 "Clinical Investigations," Research and Development Command, Office of the Surgeon General, Department of the Army, Washington, D. C.

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MATERIAL

Approximately 400 patients with pulmonary disease were seen between May, 1954 and December, 1956 on the Medical-Thoracic Surgical Services at Letterman Army Hospital, and 52 of these were subjected to thoracotomy for excision of solitary pulmonary nodules, or "coin lesions." Almost all lesions of this type were subjected to thoracotomy in line with the then prevailing practice as advocated by French *et al.*,[5] Davis *et al.*,[3] and other thoracic surgeons.

The present authors' criteria for "coin lesions" for the purpose of this report are: (1) 1 to 6 cm. in diameter; (2) rounded to ovoid with sharp, circumscribed borders; and (3) surrounded by normal appearing lung on all sides.

The majority of patients were presented at combined medical-surgical chest conferences. In each case the diagnosis was established or confirmed postoperatively by histologic means, and the histologic material was reviewed by one of us (R.S.C.). The diagnoses, symptoms, results of skin tests, results of bronchoscopic examinations, type of surgery performed, and morbidity are analyzed.

ANALYSIS OF SERIES

Table 1 shows the final histologic diagnoses, average age, and symptomatology. Malignant lesions comprise 15.4 per cent of the total. The most frequent entity is granuloma (61.5 per cent), including coccidioma, histoplasmoma, tuberculoma, and granuloma of undetermined etiology.

The etiology of the granulomas was proven by the presence of characteristic organisms in the tissue sections and/or the obtaining of characteristic cultures from the surgical material. Those granulomas classified as "of undetermined etiology" produced no growth on culture on various media used for tubercle bacilli, fungi, and other bacteria; and no organisms were identified in multiple tissue sections using hematoxylin and eosin, Gridley leucofuchsin fungus, Gomori methenamine silver, and carbolfuchsin acid-fast stains. Hamartomas accounted for 11.5 per cent of the nodular densities and chronic focal pneumonitis for 11.5 per cent.

Respiratory symptoms presented in only 3 patients, all of whom had malignant lesions. Of these, 2 had cough and hemoptysis and 1 had severe dyspnea. All others were asymptomatic.

The results of skin testing are shown in Table II and demonstrate no consistent diagnostic correlation with the final diagnosis of tuberculoma, coccidioma, or histoplasmoma; however, the results are suggestive in many cases when considered with other evidence. All patients subjected

TABLE I

DATA ON 52 CONSECUTIVE SURGICALLY REMOVED SOLITARY COIN LESIONS (1954–1956)

Pathologic Diagnosis	No. of Cases	Per Cent Total	Average Age	Symptoms Yes	Symptoms No
Granuloma					
Etiology undetermined	16	30.8	37	0	16
Coccidioma	9	17.3	38	0	9
Tuberculoma	5	9.6	41	0	5
Histoplasmoma	2	3.8	37	0	2
Chronic Focal Pneumonitis	6	11.5	38	0	6
Hamartoma	6	11.5	58	0	6
Malignancy					
Bronchogenic carcinoma	5	9.6	57	2	3
Alveolar cell carcinoma	3	5.8	50	1	2
Totals	52	99.9	44	3	49

TABLE II

POSITIVE SKIN TEST REACTION*

Pathologic Diagnosis	No. of patients	PPD†	Histo-Plasmin	Coccidi-oidin	Skin Tests Not Applied	All Skin Tests Negative
Granuloma						
Etiology undertermined	16	10	4	3	0	3
Coccidioma	9	1	2	6	0	2
Tuberculoma	5	4	0	2	‡	0
Histoplasmoma	2	1	1	0	0	1
Chronic Focal Pneumonitis	6	2	3	1	2	1
Hamartoma	6	5	1	0	0	1
Malignancy	8	4	1	0	2	2
Totals	52	27	12	12	4	10

* Histoplasmin, coccidioidin, and PPD#1 applied to all patients tested, and PPD#2 to all patients with a negative PPD#1, except as indicated.
† Purified protein derivative (tuberculoprotein) (#1 0.00002 mg., #2 0.005 mg.).
‡ PPD#2 not applied to 1 patient with negative PPD#1.

to skin tests were initially inoculated with coccidioidin, histoplasmin, and purified protein derivative #1 (PPD#1 = 0.00002 mg. of tuberculoprotein). Those with a negative PPD#1 then received PPD#2 (0.005 mg. of tuberculoprotein). Of 5 patients with proven tuberculomas who were skin tested with PPD#1, 4 were positive and 1 was negative. The negative reaction occurred in a 47 year old Negro who had a tuberculoma removed by wedge resection and acid-fast bacilli (identified as *Mycobacterium tuberculosis*) were found by smear, culture, and guinea pig inoculation of the tissue. Unfortunately, a second strength tuberculin skin test using PPD#2 was inadvertently omitted in this case.

The lesions were classified as to anatomic location within the lungs. No significant predilection for either the right or left lung was apparent. The inflammatory lesions were fairly uniformly distributed except for the 5 tuberculomas, which were all in the upper lobes. All 8 of these malignancies were upper lobe lesions. No definite conclusions can be drawn from these data with the relatively small number of cases in this series.

Bronchoscopic examination was performed on 15 patients, 8 with granulomas and 7 with malignancies. These examinations were all negative except in the case of a 64 year old male who had a bronchogenic carcinoma visibile in the left main stem bronchus. It is doubtful if this case should truly be classed as a "coin lesion" but roentgenologically this lesion met the authors' criteria and this case was previously included by French *et al.*[5] in their series. Bronchial washings were obtained in these 15 cases, and in 3 others, and were cultured for fungi and acid-fast bacilli, and examined by the Papanicolaou method. Acid-fast cultures were positive in 1 of the 5 tuberculomas and negative in the remainder, which included 1 coccidioma, 6 granuolmas of undetermined etiology, and 7 malignancies. Fungus cultures were negative in all, and the Papanicolaou smears were all negative for malignant cells, including those from the patient with the intrabronchial lesion seen on bronchoscopy.

Table III indicates the type of operation performed and the morbidity. The mortality was zero, but major complications occurred in the following 4 patients, 3 of whom had a lobectomy:

1. A 54 year old male developed massive hemorrhage and shock from intercostal arterial bleeding following a left upper

TABLE III

TYPE OF SURGERY WITH MORBIDITY AND MORTALITY DATA

Type of Surgery	No. of Cases	Major Morbidity	Mortality
Wedge Resection	44	1*	0
Lobectomy	7	3	0
Biopsy	1	0	0
Totals	52	4	0

* Severe hypotension at time of induction of anesthesia.

lobectomy for bronchogenic carcinoma. This necessitated an emergency thoracotomy. A later complication was a bronchopleural fistula.

2. A 65 year old male developed a bronchopleural fistula and empyema due to *Escherichia coli* and *Staphylococcus pyogenes*, as well as auricular fibrillation requiring digitalis and quinidine, following a right upper lobectomy for bronchogenic carcinoma.

3. A 62 year old male with hypertensive cardiovascular disease experienced hypotension and shock during the induction of anesthesia prior to surgery for a lesion of the left upper chest. Surgery was postponed until a later date when a thoracotomy and wedge excision of the lesion were performed without incident. The lesion proved to be a hamartoma.

4. A 53 year old male had been followed for 2 years in the Chest Clinic because of chronic emphysema, and subsequently a lobectomy was performed for a bronchogenic carcinoma of the right upper lobe. He developed disabling severe dyspnea and required intermittent positive pressure oxygen therapy.

Moderate and minor complications developed postoperatively in a number of other patients, lengthening the period of morbidity which is necessarily associated with any thoracotomy.

Table IV summarizes some points in the management of these patients which may be considered as medical-surgical-radiologic errors leading to unnecessary thoracotomy, or contributing to the progression of pulmonary malignancy prior to surgical intervention. These case histories, of course, are now presented with the advantage of hindsight, but it is felt that the factual data are self substantiating.

CASE 1. An asymptomatic 40 year old male had a solitary lesion in the left upper lobe, which was felt on the initial roentgenographic examination to represent a tuberculoma. Following surgery acid-fast organisms identified as *Mycobacterium tuberculosis* were found on smear, culture and guinea pig inoculation of the tissue. Prior to surgery, a tuberculin test (PPD #1) was positive, and bronchial washings revealed no acid-fast bacilli on direct smear, but

TABLE IV

ERRORS IN CASE MANAGEMENT

Case No.	Pathologic Diagnosis	Errors in Case Management
I	Tuberculoma	Failure to await cultures of bronchial washings for acid-fast bacilli in a patient with a roentgenographic impression of tuberculoma and a positive tuberculin test
II	Coccidioma	Failure to fully consider history, skin tests, complement fixation studies, and the existence of a stabilized lesion of two years' duration
III	Coccidioma	Reluctance to accept a history of a pulmonary lesion existing unchanged for 10 years together with a positive coccidiodin skin test and complement fixation studies
IV	Bronchogenic carcinoma	Uncooperative patient, irregular follow-up, and chest roentgenograms not obtained regularly for a known recent pulmonary density
V	Bronchogenic carcinoma	Pulmonary lesion missed on several chest roentgenograms

the left bronchial washings proved to be positive for *Mycobacterium tuberculosis* on culture and guinea pig inoculation. Thoracotomy with wedge excision of a lesion in the left upper lobe was performed 4 weeks after bronchoscopy, and 2 weeks prior to receipt of the results of cultures, because of concern over possible lung cancer.

Comment. In this instance bronchial washings for acid-fast bacilli were cultured and within 6 weeks proved positive. The patient, however, was subjected to thoracotomy because of the concern over possible lung cancer 4 weeks after obtaining the bronchial washings, without awaiting the results. Had the operation been postponed until the results of these cultures were known, in this patient with a roentgenologic impression of tuberculoma and a positive tuberculin test, surgical intervention could have been avoided and a more conservative medical regimen adopted.

CASE II. A 24 year old asymptomatic male had a solitary nodule in the left upper lobe. Histologic studies later revealed this to be a coccidioma. He had lived in an area endemic for coccidioidomycosis. Two years previously (1953) he had been evaluated in Arizona because of the same roentgenographic density, and a diagnosis of coccidioidomycosis, arrested, was made on the basis of a strongly positive coccidioidin skin test and negative skin tests for tuberculosis and histoplasmosis. On routine annual roentgenograms (1955), the density in the upper lung field was again noted. A repeat skin test for coccidioidomycosis was again strongly positive and tuberculin and histoplasmin skin tests were negative. The complement fixation test for coccidioidomycosis was positive in a low titer. A review of previous chest roentgenograms revealed no progression of the density between 1953 and 1955. A wedge resection of the nodule was performed.

Comment. It would appear that with the well documented evidence of a clinical diagnosis of coccidioidomycosis in this young individual the surgical intervention was not indicated, especially for a stabilized granuloma.

CASE III. A 65 year old male presented on roentgenograms a nodular density in the left upper lobe, later proven to be a coccidioma. The lesion was known to have been present for 11 years previously on the basis of annual chest roentgenograms between 1945 and 1956. Documented roentgenologic reports revealed the lesion to be unchanged. The complement fixation test was positive for coccidioidomycosis in a low titer, and the skin test was strongly positive. Because of the feeling that the lesion could represent a malignancy, he was subjected to a thoracotomy with wedge excision, and a coccidioma was removed.

Comment. It would appear that this patient had a well documented clinical diagnosis of coccidioidomycosis with a stabilized lesion and that surgical intervention was unnecessary.

CASE IV. A 52 year old male had been receiving periodic pneumoperitoneum refills for tuberculosis of the right upper lobe from 1951 to 1953. In addition, he had received antituberculous drugs. The pneumoperitoneum was terminated in May, 1953 as the disease was considered arrested. At the time of the final peritoneal refill, a small irregular roentgenographic density was noted in the left midlung field, but was not considered significant. No repeat chest roentgenograms were obtained between May, 1953 and July, 1954 because of lack of cooperation by the patient. In July, 1954 roentgenograms revealed a nodular opacity at the site of the previous small irregular density. A thoracotomy followed by a lobectomy was performed, and the lesion proved to be a bronchogenic carcinoma of the squamous cell type. The patient is alive 3 years postoperatively, but is dyspneic and has spread of his disease, demonstrated by new nodular densities appearing in the lung fields.

Comment. The diagnosis of bronchogenic carcinoma in this patient was missed when the irregular density originally appeared on the chest roentgenogram, and adequate follow-up of a new nodular density in the lung was not obtained. The importance of careful roentgenographic follow-up of pulmonary densities is emphasized, although the outcome in this particular instance might not have been altered.

CASE V. A 53 year old male had been followed in Chest Clinics from 1954 to 1956 and treated for pulmonary emphysema. In 1956 a density was noted on his chest roentgenogram, partially obscured by the right clavicle. Review of the previous roentgenograms revealed that this had been present for many months but had been overlooked. A lordotic roentgenogram resulted in excellent visualization of the lesion. A right

upper lobe lobectomy was performed and the lesion proved to be a bronchogenic carcinoma. Approximately 1 year postoperatively, this patient was in a terminal status with extensive metastatic spread.

Comment. The nodular density which subsequently proved to be a bronchogenic carcinoma was missed in this patient who had been seen on numerous occasions for pulmonary emphysema. Again the potential importance of finding pulmonary lesions early is emphasized.

PREOPERATIVE DIAGNOSTIC EVALUATION OF SERIES BY FIFTEEN SPECIALISTS

To ascertain the possible accuracy of preoperative diagnosis and the pattern of selection of patients for thoracotomy, sets of preoperative chest roentgenograms were obtained on 50 of the 52 patients in the series. These, together with protocols containing all the information available prior to surgical intervention, were submitted to a group of established specialists including 5 radiologists, 5 thoracic surgeons, and 5 internists specializing in diseases of the chest. The following questionnaire was submitted:

1. Does the lesion conform to your interpretation of a coin lesion?
2. What is your preoperative diagnosis?
   (a) Is the lesion inflammatory?
   (b) Is the lesion a benign tumor?
   (c) Is the lesion malignant?
   (d) Does it represent an anomaly?
3. Would you recommend surgical removal?
4. What is your indication for such surgical removal?
   (a) For diagnosis?
   (b) For cure of localized tumor?
   (c) For cure of localized inflammatory disease?
5. What additional diagnostic studies would you request in addition to the chest films and those contained in the protocol?

The answers given by the participating specialists to the questionnaire are tabulated in Tables V, VI, VIII, and IX.

The responses to the first question "DOES THE LESION CONFORM TO YOUR INTERPRETATION OF A COIN LESION?" are shown in Table V. Of the granulomatous lesions the majority of the reviewers felt that 11 out of the 16 granulomas of undetermined etiology represented "coin lesions," while 7 of the 8 coccidiomas, 3 of the 5 tuberculomas, 1 of the 2 histoplasmomas; 4 of the 6 foci of chronic pneumonitis; 4 of the 5 hamartomas; and none of the 8 malignancies were considered typical "coin lesions." There appeared to be no notable difference between the opinions of the radiologists, surgeons, and internists.

The responses to the second question "WHAT IS YOUR PREOPERATIVE DIAGNOSIS?" are shown in Table VI. The inflammatory lesions were considered to be such by 88 per cent of all of the reviewers (95 per cent of the radiologists, 82 per cent of the surgeons, and 88 per cent of the internists). There were only a few who felt that some of these lesions represented a benign or malignant tumor or an anomaly.

In the malignant lesions, there was decided variation in the preoperative diagnoses. The *majority* of the radiologists favored malignancy in all 8 cases, the *majority* of the surgeons in 6 of the 8, but the *majority* of the internists in only 4 of the 8. Over-all, 70 per cent of the reviewers favored the diagnosis of malignancy in this group (75 per cent of the radiologists, 71 per cent of the surgeons, and 65 per cent of the internists). In this proved group of malignancies, the second diagnostic choice was inflammatory lesion, favored by 27 per cent of all of the reviewers (17 per cent of the radiologists, 27 per cent of the surgeons, and 35 per cent of the internists). The remaining 3 per cent of the specialists considered the lesions benign tumor or anomaly.

In the 5 hamartomas, the diagnoses were inflammatory lesion (57 per cent) and malignancy (39 per cent). Seventy-two per cent of the radiologists felt that these lesions were inflammatory and 24 per cent that they were malignant. Both the surgeons' and internists' opinions were divided almost evenly between these two groups.

TABLE V

DOES THIS LESION CONFORM TO YOUR INTERPRETATION OF A COIN LESION?

Pathologic Diagnosis	Radiologists		Surgeons		Internists		Whole Group		
	Yes	No	Yes	No	Yes	No	Yes	No	Consensus on Diagnosis As Coin Lesion
Granuloma (31)									
Granuloma of Undetermined Etiology (16)									
G1	2	3	3	2	1	4	6	9	No
G2	2	3	–	5	1	4	3	12	No
G3	5	–	4	1	5	–	14	1	Yes
G4	5	–	3	2	5	–	13	2	Yes
G5	5	–	3	2	5	–	13	2	Yes
G6	1	4	2	3	3	2	6	9	No
G7	–	5	3	2	–	5	3	12	No
G8	5	–	5	–	4	1	14	1	Yes
G9	5	–	5	–	5	–	15	–	Yes
G10	5	–	2	3	2	3	9	6	Yes
G11	5	–	3	2	4	1	12	3	Yes
G12	4	1	5	–	4	1	13	2	Yes
G13	5	–	4	1	4	1	13	2	Yes
G14	4	1	4	1	3	2	11	4	Yes
G15	1	4	2	3	1	4	4	11	No
G16	5	–	5	–	5	–	15	–	Yes
	59	21	53	27	52	28	164	76	Yes 11, No 5
Coccidioma (8)									
C1	5	–	3	2	5	–	13	2	Yes
C2	5	–	5	–	4	1	14	1	Yes
C3	5	–	5	–	5	–	15	–	Yes
C4	4	1	5	–	5	–	14	1	Yes
C5	4	1	3	2	3	2	10	5	Yes
C6	–	5	2	3	–	5	2	13	No
C7	5	–	4	1	4	1	13	2	Yes
C8	5	–	4	1	5	–	14	1	Yes
	33	7	31	9	31	9	95	25	Yes 7, No 1
Tuberculoma (5)									
T1	–	5	2	3	–	5	2	13	No
T2	5	–	5	–	4	1	14	1	Yes
T3	–	5	2	3	2	3	4	11	No
T4	5	–	5	–	5	–	15	–	Yes
T5	2	3	5	–	4	1	11	4	Yes
	12	13	19	6	15	10	46	29	Yes 3, No 2
Histoplasmoma (2)									
H1	1	4	3	2	3	2	7	8	No
H2	4	1	5	–	3	2	12	3	Yes
	5	5	8	2	6	4	19	11	Yes 1, No 1

TABLE V (*Continued*)

DOES THIS LESION CONFORM TO YOUR INTERPRETATION OF A COIN LESION?

Pathologic Diagnosis	Radiologists		Surgeons		Internists		Whole Group		
	Yes	No	Yes	No	Yes	No	Yes	No	Consensus on Diagnosis As Coin Lesion
Chronic Focal Pneumonitis (6)									
P1	5	–	5	–	5	–	15	–	Yes
P2	–	5	1	4	2	3	3	13	No
P3	5	–	3	2	4	1	12	3	Yes
P4	4	1	4	1	5	–	13	2	Yes
P5	1	4	–	5	1	4	2	13	No
P6	5	–	4	1	4	1	13	2	Yes
	20	10	17	13	21	9	58	32	Yes 4, No. 2
Hamartoma (5)									
H1	3	2	1	4	2	3	6	9	No
H2	5	–	5	–	4	1	14	1	Yes
H3	4	1	5	–	5	–	14	1	Yes
N4	2	3	4	1	3	2	9	6	Yes
H5	5	–	5	–	5	–	15	–	Yes
	19	6	20	5	19	6	58	17	Yes 4, No 1
Malignancy (8)									
Bronchogenic Carcinoma (5)									
M1	1	4	–	5	2	3	3	12	No
M2	1	4	–	5	–	5	1	14	No
M3	–	5	1	4	–	5	1	14	No
M4	–	5	2	3	1	4	3	12	No
M5	–	5	1	4	–	5	1	14	No
Alveolar Cell Carcinoma (3)									
M6	2	3	2	3	2	3	6	9	No
M7	–	5	1	4	2	3	3	12	No
M8	–	5	1	4	1	4	2	13	No
	4	36	8	32	8	32	20	100	Yes 0, No 8

No reviewers called any of these lesions anomalies, and only 3 of the 75 diagnoses were benign tumor. It is to be noted that the hamartomas are the only group of benign lesions with a significant question as to malignancy in this series.

It is noteworthy that the diagnoses of benign tumor, anomaly, and malignant tumor among the inflammatory lesions are very infrequent and widely scattered, except for 1 case of granuloma of undetermined etiology which 3 of the 5 surgeons called malignant.

The responses to the third question "WOULD YOU RECOMMEND SURGICAL REMOVAL"? are shown in Table VII. Of the granulomas of undetermined etiology, 7 out of 16 lesions would have been surgically removed, based on the *majority* opinion of the group of reviewers. Of 6 lesions later found to be chronic focal areas of pneumonitis, 2 would have been removed by

TABLE VI

WHAT IS YOUR PREOPERATIVE DIAGNOSIS?

Pathologic Diagnosis	Radiologists				Surgeons				Internists				Whole Group		
	Inflammatory Lesion	Benign Tumor	Malignant Tumor	Anomaly	Inflammatory Lesion	Benign Tumor	Malignant Tumor	Anomaly	Inflammatory Lesion	Benign Tumor	Malignant Tumor	Anomaly	Benign	Malignant	Majority Consensus on Malignancy
Granuloma (31)															
Granuloma of Undetermined Etiology (16)															
G1	5	–	–	–	4	1	–	–	5	–	–	–	15	–	Benign
G2	4	1	–	–	5	–	–	–	5	–	–	–	15	–	Benign
G3	5	–	–	–	3	2	–	–	3	1	1	–	14	1	Benign
G4	4	–	–	1	5	–	–	–	5	–	–	–	15	–	Benign
G5	5	–	–	–	5	–	–	–	5	–	–	–	15	–	Benign
G6	5	–	–	–	4	1	–	–	5	–	–	–	15	–	Benign
G7	5	–	–	–	4	–	–	1	5	–	–	–	15	–	Benign
G8	5	–	–	–	5	–	–	–	4	–	1	–	14	1	Benign
G9	5	–	–	–	4	–	1	–	4	–	1	–	13	2	Benign
G10	5	–	–	–	3	1	1	–	4	1	–	–	14	1	Benign
G11	5	–	–	–	3	1	–	1	3	–	1	1	14	1	Benign
G12	5	–	–	–	5	–	–	–	5	–	–	–	15	–	Benign
G13	5	–	–	–	5	–	–	–	5	–	–	–	15	–	Benign
G14	5	–	–	–	4	–	1	–	4	–	1	–	13	2	Benign
G15	5	–	–	–	5	–	–	–	5	–	–	–	15	–	Benign
G16	3	1	1	–	1	1	3	–	4	1	–	–	11	4	Benign
	76	2	1	1	65	7	6	2	71	3	5	1	228	12	Benign–16
Coccidioma (8)															
C1	5	–	–	–	4	1	–	–	5	–	–	–	15	–	Benign
C2	5	–	–	–	5	–	–	–	5	–	–	–	15	–	Benign
C3	5	–	–	–	5	–	–	–	4	–	1	–	14	1	Benign
C4	5	–	–	–	5	–	–	–	5	–	–	–	15	–	Benign
C5	4	1	–	–	3	1	1	–	3	2	–	–	14	1	Benign
C6	5	–	–	–	5	–	–	–	5	–	–	–	15	–	Benign
C7	5	–	–	–	4	–	1	–	4	–	1	–	13	2	Benign
C8	5	–	–	–	3	2	–	–	5	–	–	–	15	–	Benign
	39	1	–	–	34	4	2	–	36	2	2	–	116	4	Benign–8
Tuberculoma (5)															
T1	5	–	–	–	5	–	–	–	5	–	–	–	15	–	Benign
T2	5	–	–	–	5	–	–	–	4	–	1	–	14	1	Benign
T3	3	1	1	–	4	–	1	–	5	–	–	–	13	2	Benign
T4	5	–	–	–	5	–	–	–	4	–	1	–	14	1	Benign
T5	5	–	–	–	2	1	1	1	4	–	1	–	13	2	Benign
	23	1	1	–	21	1	2	1	22	–	3	–	69	6	Benign–5

Table VI (*Continued*)

Pathologic Diagnosis	Radiologists				Surgeons				Internists				Whole Group		
	Inflammatory Lesion	Benign Tumor	Malignant Tumor	Anomaly	Inflammatory Lesion	Benign Tumor	Malignant Tumor	Anomaly	Inflammatory Lesion	Benign Tumor	Malignant Tumor	Anomaly	Benign	Malignant	Majority Consensus on Malignancy
Histoplasmoma (2)															
H1	5	–	–	–	5	–	–	–	5	–	–	–	15	–	Benign
H2	5	–	–	–	3	1	1	–	4	1	–	–	14	1	Benign
	10	–	–	–	8	1	1	–	9	1	–	–	29	1	Benign–2
Chronic Focal Pneumonitis (6)															
P1	4	1	–	–	4	–	1	–	3	1	1	–	13	2	Benign
P2	4	1	–	–	3	1	1	–	5	–	–	–	14	1	Benign
P3	5	–	–	–	4	1	–	–	5	–	–	–	15	–	Benign
P4	5	–	–	–	5	–	–	–	4	1	–	–	15	–	Benign
P5	4	1	–	–	5	–	–	–	4	1	–	–	15	–	Benign
P6	5	–	–	–	2	1	2	–	4	–	1	–	12	3	Benign
	27	3	–	–	23	3	4	–	25	3	2	–	84	6	Benign–6
Hamartoma (5)															
H1	3	–	2	–	1	–	4	–	1	–	4	–	5	10	*Malignant
H2	3	–	2	–	1	–	4	–	1	–	4	–	5	10	*Malignant
H3	4	–	1	–	4	–	1	–	5	–	–	–	13	2	Benign
H4	3	1	1	–	3	–	2	–	3	–	2	–	10	5	†Benign
H5	5	–	–	–	3	2	–	–	3	–	2	–	13	2	Benign
	18	1	6	–	12	2	11	–	13	–	12	–	46	29	*Malignant–2 Benign–3 (1 †)
Malignancy (8)															
Bronchogenic Carcinoma (5)															
M1	–	1	4	–	–	–	5	–	–	–	5	–	1	14	*Malignant
M2	1	1	3	–	2	–	3	–	4	–	1	–	8	7	*Benign
M3	1	–	4	–	2	–	3	–	3	–	2	–	6	9	*Malignant
M4	2	–	3	–	4	–	1	–	4	–	1	–	10	5	†Benign
M5	–	–	5	–	–	–	5	–	–	–	5	–	–	15	*Malignant
Alveolar Cell Carcinoma (3)															
M6	1	–	4	–	–	–	5	–	–	–	5	–	1	14	*Malignant
M7	2	–	3	–	3	–	2	–	3	–	2	–	8	7	*Benign
M8	–	1	4	–	–	–	5	–	–	–	5	–	1	14	*Malignant
	7	3	30	–	11	–	29	–	14	–	26	–	38	85	*Malignant–5 Benign–3 (1 †)

* *Less than two-thirds* of the participating specialists diagnose the lesion as benign, therefore surgical intervention is indicated.
† *Exactly two-thirds* (10/15) of the participating specialists diagnose the lesion as benign, therefore surgical intervention is strongly considered.
All of the other lesions were considered benign by *more than two-thirds* of the participating specialists.

TABLE VII

THEORETIC PROBABILITY OF CALLING MALIGNANT LESIONS BENIGN OR BENIGN LESIONS MALIGNANT BASED ON THE RECOMMENDED CRITERIA FOR A MEDICAL-SURGICAL-RADIOLOGIC CHEST CONFERENCE

Criterion	Malignant Lesions Called Benign		Benign Lesions Called Malignant	
	No. of Consultants			
	6	15	6	15
	Probability*			
Two-thirds or more interpreting lesion as benign	0.0628	0.0028	0.0118	0.0011
More than two-thirds interpreting lesion as benign	0.0093	0.0005	0.0952	0.0082

* Probabilities are based on the binomial probability distribution where it is assumed that the probability of calling a case malignant when benign is 0.09 and the probability of calling a case benign when malignant is 0.29.

surgery and 4 rejected, while of the 5 tuberculomas, 2 histoplasmomas, and 5 hamartomas all would have been surgically removed. There were 8 lesions later proven to be coccidiomas and in 4 of these surgery was recommended. Of the 8 cases of malignant lesions, surgery was recommended in 7. The patient in whom surgery was not advised (M8) had a history of a previously proven malignancy of the left lung, and he later developed the "coin lesion" under consideration in his right lung. It is noted that only 32 of the 50 patients in the study would have been selected for thoracotomy by a simple *majority* of this group of reviewers.

The over-all selection for thoracotomy, independent of the preoperative diagnostic impression, by the *majority* of the surgeons was 78 per cent (39 out of 50), compared with 46 per cent (23 out of 50) by the radiologists and 34 per cent (17 out of 50) by the internists. In the cases of inflammatory lesions, surgery was recommended most often by the surgeons (27 out of 37, compared with 13 out of 37 by the radiologists, 7 out of 37 by the internists, and 20 out of 37 by the *majority* of the combined group). In the malignant lesions, it is noted that the surgeons selected 7 out of 8 for thoracotomy, the same as the radiologist, but the internists selected only 5 of the 8.

The responses to the fourth question "WHAT IS YOUR INDICATION FOR SURGICAL REMOVAL?" are shown in Table IX. The principal reason listed for surgical intervention in the case of the lesions which later proved to be inflammatory (granuloma of undetermined etiology, tuberculoma, histoplasmoma, coccidioma, and chronic focal pneumonitis) was "for diagnosis," which greatly predominated over "for cure of localized tumor." In lesions later shown to be hamartoma, there was almost an even split among the reviewers between "for cure of localized tumor" and "for diagnosis," and it should be noted that these were diagnosed either as inflammatory lesions or malignant tumors (Table VI). Of the subsequently proven malignant lesions, the recommendation for removal "for cure of localized tumor" exceeded "for diagnosis" by approximately 4 to 1, and these were correctly diagnosed preoperatively as malignancies by the same ratio. "For cure of localized inflammatory disease" was infrequently listed as a reason for surgery (about 1 per cent).

The responses to the last question "WHAT ADDITIONAL DIAGNOSTIC STUDIES WOULD YOU REQUEST IN ADDITION TO THE CHEST FILMS AND THOSE CONTAINED IN THE PROTOCOL?" are too voluminous to tabulate. Most of the protocols and the accompanying chest roentgenograms were considered adequate

for an accurate appraisal. On individual cases many of the reviewers requested such additional information as follows: (1) laminagrams to demonstrate the presence of irregularities of calcifications in the density; (b) skin tests including tuberculin, histoplasmin, and coccidioidin on the few patients who had not had them; (c) complement fixation tests on all patients having positive coccidioidin or histoplasmin skin tests; (d) bronchoscopic examination prior to surgical intervention; (e) cytologic studies on the sputum when malignancy was suspected; (f) gastric washings and/or sputum studies for acid-fast bacilli on patients with positive tuberculin skin tests; (g) scalene lymph node biopsy, when malignancy was suspected; (h) angiograms when congenital anomalies of the lung were suspected; and (i) intravenous pyelograms and/or gastrointestinal roentgenographic studies in suspected metastatic lesions from the kidney, gastrointestinal tract, or pancreas. These additional procedures were requested so that an accurate diagnosis could be made and thereby the need for surgery better determined. Since in this series thoracotomy was the rule, some otherwise indicated preoperative tests were omitted in the work-ups.

DISCUSSION

The indications for surgical excision of asymptomatic solitary pulmonary lesions are reported to be the high incidence of malignancy, and the low operative mortality and morbidity. The indications for surgical excision of known inflammatory lesions (which are usually focal manifestations of systemic disease and which comprised 73 per cent of the solitary nodules of this series) are not clear. Mitchell[18] reported that 25 per cent of one series of patients with tuberculomas treated conservatively prior to drug therapy had further progression of their disease. In other series[1,4,14,17] followed for 6 months to 15 years, there was a relapse rate ranging from 7 per cent to 30 per cent. It should be emphasized that in Mitchell's cases, and in the others reported, all patients were known to have had prior active pulmonary tuberculosis and had been treated without specific antituberculous therapy, the tuberculomas being late manifestations. This is in contradistinction to the patient with a solitary nodule of the lung having no history identifying his disease as arrested pulmonary tuberculosis at the time of the discovery of the solitary lesion, as was the case with the patients in this series.

There are no references regarding the incidence of progression of coccidiomas or histoplasmomas. Winn[21] has a conservative attitude about the management of the cavitary lesions of coccidioidomycosis, and states that he has never seen dissemination or spread from person to person. He advises surgical removal for complications such as hemorrhage, pneumonitis, pleural effusion, and abscess formation. One could conclude that such a conservative attitude toward the cavity of coccidioidomycosis would lead to a still more conservative attitude with regard to the solitary nodule of the disease. Hinshaw and Garland[10] likewise advocate a conservative policy and state that in the San Joaquin Valley of California less than 1 per cent of such solitary lesions prove to be malignant.

In regard to the histoplasmoma, no references are available regarding the incidence of progression. The relative infrequency of the acute forms of histoplasmosis[2,6,11,12,16] when compared with the high incidence of pulmonary calcifications, negative tuberculin skin tests, and positive skin tests for histoplasmosis would appear to be a contraindication for surgical excision of all "coin lesions," at least in endemic areas such as the Mississippi Valley.

Reports dealing with granulomas of undetermined etiology (most of which undoubtedly represent "burned out" tuberculomas, histoplasmomas, or coccidiomas), areas of chronic focal pneumonitis, and hamartomas are likewise not well documented as to their progression, either clinically or roentgenologically. There is

TABLE VIII

WOULD YOU RECOMMEND SURGICAL REMOVAL?

Pathologic Diagnosis	Radiologists		Surgeons		Internists		Whole Group		
	Yes	No	Yes	No	Yes	No	Yes	No	*Majority* Consensus on Surgical Removal
Granuloma (31)									
Granuloma of Undetermined Etiology (16)									
G1	2	3	5	–	3	2	10	5	†Yes
G2	1	4	–	5	1	4	2	13	No
G3	1	4	4	1	5	–	10	5	†Yes
G4	2	3	4	1	2	3	8	7	Yes
G5	–	5	2	3	–	5	2	13	No
G6	2	3	4	1	1	4	7	8	No
G7	–	5	3	2	1	4	4	11	No
G8	1	4	3	2	2	3	6	9	No
G9	–	5	2	3	2	3	4	11	No
G10	2	3	2	3	2	3	6	9	No
G11	1	4	4	1	4	1	9	6	Yes
G12	1	4	3	2	1	4	5	10	No
G13	1	4	2	3	–	5	3	12	No
G14	2	3	4	1	2	3	8	7	Yes
G15	3	2	5	–	2	3	10	5	†Yes
G16	4	1	4	1	1	4	9	6	Yes
	23	57	51	29	29	51	103	137	Yes 7, No 9
Coccidioma (8)									
C1	–	5	5	–	1	4	6	9	No
C2	–	5	4	1	–	5	4	11	No
C3	1	4	4	1	2	3	7	8	No
C4	1	4	2	3	–	5	3	12	No
C5	3	2	5	–	2	3	10	5	†Yes
C6	3	2	4	1	1	4	8	7	Yes
C7	2	3	5	–	2	3	9	6	Yes
C8	3	2	5	–	2	3	10	5	†Yes
	13	27	34	6	10	30	57	63	Yes 4, No 4
Tuberculoma (5)									
T1	3	2	5	–	1	4	9	6	Yes
T2	3	2	5	–	4	1	12	3	*Yes
T3	5	–	5	–	4	1	14	1	*Yes
T4	4	1	5	–	2	3	11	4	*Yes
T5	2	3	4	1	2	3	8	7	Yes
	17	8	24	1	13	12	54	21	Yes 5, No 0
Histoplasmoma (2)									
H1	4	1	4	1	2	3	10	5	†Yes
H2	5	–	3	2	3	2	11	4	*Yes
	9	1	7	3	5	5	21	9	Yes 2, No 0

TABLE VIII (*Continued*)

WOULD YOU RECOMMEND SURGICAL REMOVAL?

Pathologic Diagnosis	Radiologists		Surgeons		Internists		Whole Group		
	Yes	No	Yes	No	Yes	No	Yes	No	*Majority* Consensus on Surgical Removal
Chronic Focal Pneumonitis (6)									
P1	3	2	5	–	4	1	12	3	*Yes
P2	1	4	2	3	1	4	4	11	No
P3	1	4	2	3	–	5	3	12	No
P4	1	4	2	3	–	5	3	12	No
P5	2	3	2	3	2	3	6	9	No
P6	3	2	4	1	2	3	9	6	Yes
	11	19	17	13	9	21	37	53	Yes 2, No 4
Hamartoma (5)									
H1	2	3	4	1	4	1	10	5	†Yes
H2	4	1	5	–	4	1	13	2	*Yes
H3	3	2	3	2	3	2	9	6	Yes
H4	2	3	3	2	3	2	8	7	Yes
H5	4	1	5	–	5	–	14	1	*Yes
	15	10	20	5	19	6	54	21	Yes 5, No 0
Malignancy (8)									
Bronchogenic Carcinoma (5)									
M1	5	–	5	–	5	–	15	–	*Yes
M2	5	–	3	2	2	3	10	5	†Yes
M3	5	–	4	1	3	2	12	3	*Yes
M4	5	–	1	4	2	3	8	7	Yes
M5	5	–	5	–	5	–	15	–	*Yes
Alveolar Cell Carcinoma (3)									
M6	5	–	5	–	5	–	15	–	*Yes
M7	4	1	5	–	3	2	12	3	*Yes
M8	2	3	4	1	1	4	7	8	‡No
	36	4	32	8	26	14	94	26	Yes 7, No 1

* *More than two-thirds* of the specialists favor thoracotomy.
† *Exactly two-thirds* of the specialists favor thoracotomy.
‡ Previously diagnosed malignancy in other lung.

evidence that some of the areas of localized chronic pneumonitis may result in segmental atelectasis and, therefore, surgical removal may be indicated. It appears probable, however, that such nonresolving cases are exceptional, and the surgery is not then for removal of a "coin lesion."

If it is believed that solitary pulmonary densities should be surgically removed, it appears obvious that there are some instances where an early diagnosis as to the type of density may be made with a high degree of certainty. Such instances are illustrated in Cases II and III in Table IV.

In order to evaluate the possible accuracy of preoperative diagnosis, a questionnaire was submitted to 15 specialists in the field of chest disease, together with the chest roentgenograms and preoperative clinical protocols of 50 patients, and the responses reveal some very interesting data. The term "coin lesion" does not have a specific meaning and the term should probably be avoided, or if used must be carefully and explicitly defined. The cases in this series fulfill the present authors' rather broad criteria for "coin lesions" and the divergence of opinion among the 15 specialists clearly illustrates the lack of a uniform meaning of the term "coin lesion." It is important to note that the inflammatory lesions were considered "coin lesions" in most cases, with the coccidiomas and hamartomas most often fulfilling the apparently different criteria of the various reviewers. It appears significant that none of the malignancies were considered "coin lesions" by the majority of reviewers, although they fulfilled the authors' criteria, and most of them were included in the series of French *et al.*[5] This would suggest that most such malignant "coin lesions" have different characteristics than most benign lesions, but when compared with the preoperative diagnoses (Table VI) no such clear-cut differences are apparent. This indicates a lack of significance of the concept of a "coin lesion" in this sense. The marked split of individual opinion on each lesion, and between lesions, again indicates the lack of any universal meaning of the term "coin lesion."

When this series of reasonably complete protocols and chest roentgenograms of patients with solitary pulmonary nodules was presented to a group of well qualified internists, surgeons, and radiologists, a high degree of preoperative diagnostic accuracy of malignancy versus nonmalignancy was achieved. In the entire group of 50 cases the *majority* opinion of the radiologists was correct regarding malignancy or nonmalignancy, while the *majority* of the surgeons missed 5 (2 hamartomas called malignant, 2 malignancies called nonmalignant, and one granuloma called malignant), and the *majority* of the internists missed 6 (4 malignancies called nonmalignant, including the same 2 called nonmalignant by the surgeons; and the same 2 hamartomas called malignant by the surgeons). It should be emphasized that in 19 of the 37 inflammatory lesions all 15 reviewers *unanimously* called the lesion nonmalignant, but the 5 radiologists *unanimously* agreed on 29 of the 37. Of the inflammatory lesions as a group, agreement was generally excellent with no more than 4 considering any one lesion malignant. The opinions in the cases of the hamartomas and malignancies were much more divided. Based on the opinions in this series, the significantly better performance of the radiologists compared with that of the surgeons and internists should be noted, emphasizing the importance of the interpretation of roentgenograms and of thorough training in this area.

When the impression of nonmalignancy was held by *more than two-thirds* (11 or more) of the reviewing physicians, it was invariably correct, and this was the case in 37 out of the 37 inflammatory lesions and in 2 of the 5 hamartomas, but in none of the 8 malignancies. The *majority* opinion had a poor correlation with the actual diagnosis in the case of the hamartomas and malignancies, but was also uniformly correct in the case of all of the inflammatory lesions. The area of greatest difficulty centered in calling the hamartomas malignant and in failing to recognize some malignancies. Only 5 of the 8 malignant lesions were correctly diagnosed by the *majority* of the reviewers, yet in none of these cases did *more than two-thirds* of the reviewers make the error.

Thus, using the criterion that a lesion will be considered malignant unless *more than two-thirds* (11 or more) of the reviewers call it nonmalignant, all of the malignancies would have been considered malignant in this series and only 3 benign lesions (all hamartomas, H1, H2, H4) would have been called malignant. If a lesser criterion of *two-*

thirds or more (10 or more) of the reviewers calling a lesion nonmalignant were adopted, 1 of the 8 malignancies (M_4) would have been considered benign and missed, and only 2 of the hamartomas (H_1, H_2) would have been considered malignant. No significant question arises concerning any of the inflammatory lesions using either of these criteria, all of them being overwhelmingly considered nonmalignant.

On the basis of these data, it is concluded that if a 6 member medical-surgical-radiologic chest conference, consisting preferably of 2 members from each specialty, is established, it would be able to accurately diagnose solitary pulmonary nodules or "coin lesions" as to malignancy or nonmalignancy. Either the criterion of *more than two-thirds* (5 or more) of the members agreeing a lesion is not malignant, or one of *two-thirds or more* (4 or more) agreeing, is indicated by these data. A stastitical analysis of the interpretation of this series on these bases by a medical-surgical-radiologic chest conference is given in Table VII. This analysis is based on 630 total evaluations of the benign lesions which were 91 per cent correct, and on 120 ovaluations of the malignant lesions which were 71 per cent correct. The interpretation of these data is that with 6 consultants, and using the criterion that *more than two-thirds* (5 or more) must call a lesion benign, there is a 0.9 per cent chance that a malignant lesion will be misdiagnosed as benign. Using the criterion of *two-thirds or more* (4 or more), there is a 6.28 per cent chance of error. Since the less chance taken on missing a malignancy the greater the number of benign lesions considered possibly malignant, the corresponding chances of calling a benign lesion malignant are 9.52 per cent and 1.18 per cent, and most of these lesions will be hamartomas with only a very rare inflammatory lesion misdiagnosed as malignant. This may seem to be a narrow margin on which to work, but it should be emphasized again that one-half of the inflammatory lesions were regarded as benign by all 15 reviewers in this series, and the remaining half were regarded as malignant by only 1 to at most 4 reviewers. Thus, whatever reasonable criteria one desires to establish, the inflammatory solitary pulmonary nodules will be called benign by the great majority of the members of such a conference and quite clearly separated from the malignancies and most of the hamartomas. It is far better to make any errors in favor of diagnosing the maximum number of malignancies, even if a somewhat greater number of benign lesions are preoperatively felt to be suspicious for malignancy, and therefore the authors' recommended criterion is that a lesion should be considered malignant unless *more than two-thirds* (5 or more of a 6 man conference) of the reviewers feel it is benign. This will result in a correct diagnosis of 99 per cent of the malignancies and 90 per cent of the benign lesions, with most of the errors occurring in the relatively small group of hamartomas.

With 15 consultants, the errors should be markedly reduced but a conference of this size is impractical. Examination of the statistical data in Table VII for 15 reviewers would suggest that in a series of the size of the one presented no errors would be made, yet, using the *more than two-thirds* criterion, 2 hamartomas were diagnosed as malignant. Inspection of the data in Table VI immediately reveals that the hamartomas form a special group with many characteristics that cause them to be considered malignant. The inhomogeneity of the benign group produces this paradox, but makes the statistical conclusions even more valid for the inflammatory lesions which constitute the great majority of the benign lesions. It becomes apparent that preoperatively about 50 per cent of the hamartomas will be considered to be malignancies. The diagnostic error indicated by these data is considerably less than that of many fully accepted diagnostic procedures, and on this basis it is felt that only a few selected solitary pulmonary nodules ("coin lesions") need be resected.

TABLE IX

WHAT IS YOUR INDICATION FOR SURGICAL REMOVAL?

Pathologic Diagnosis	Radiologists				Surgeons				Internists			
	Would Not Operate	For Diagnosis	For Cure of Localized Tumor	For Cure of Localized Inflammatory Disease	Would Not Operate	For Diagnosis	For Cure of Localized Tumor	For Cure of Localized Inflammatory Disease	Would Not Operate	For Diagnosis	For Cure of Localized Tumor	For Cure of Localized Inflammatory Disease
Granuloma (31)												
Granuloma of Undetermined Etiology (16)												
G1	3	2	–	–	–	5	–	–	2	3	–	–
G2	4	1	–	–	5	–	–	–	4	1	–	–
G3	4	1	–	–	1	4	–	–	–	4	1	–
G4	3	2	–	–	1	4	–	–	3	2	–	–
G5	5	–	–	–	3	2	–	–	5	–	–	–
G6	3	2	–	–	1	4	–	–	4	1	–	–
G7	5	–	–	–	2	3	–	–	4	1	–	–
G8	4	1	–	–	2	3	–	–	3	1	1	–
G9	5	–	–	–	3	1	1	–	3	1	1	–
G10	3	2	–	–	3	1	1	–	3	2	–	–
G11	4	1	–	–	1	4	–	–	1	3	1	–
G12	4	1	–	–	2	3	–	–	4	1	–	–
G13	4	1	–	–	3	2	–	–	5	–	–	–
G14	3	2	–	–	1	3	1	–	3	1	1	–
G15	2	3	–	–	–	5	–	–	3	2	–	–
G16	1	3	1	–	1	1	3	–	4	1	–	–
	57	22	1	–	29	45	6	–	51	24	5	–
Coccidioma (8)												
C1	5	–	–	–	–	5	–	–	4	1	–	–
C2	5	–	–	–	1	4	–	–	5	–	–	–
C3	4	1	–	–	1	4	–	–	3	1	1	–
C4	4	1	–	–	3	2	–	–	5	–	–	–
C5	2	3	–	–	–	4	1	–	3	2	–	–
C6	2	2	–	1	1	1	–	3	4	–	–	1
C7	3	1	–	1	–	5	–	–	3	–	2	–
C8	2	3	–	–	–	5	–	–	3	2	–	–
	27	11	–	2	6	30	1	3	30	6	3	1
Tuberculoma (5)												
T1	2	3	–	–	–	5	–	–	4	1	–	–
T2	2	3	–	–	–	4	–	1	1	4	–	–
T3	–	4	1	–	–	4	1	–	1	4	–	–
T4	1	2	–	2	–	5	–	–	3	2	–	–
T5	3	1	–	1	1	4	–	–	3	1	1	–
	8	13	1	3	1	22	1	1	12	12	1	–

TABLE IX (*Continued*)

Pathologic Diagnosis	Radiologists				Surgeons				Internists			
	Would Not Operate	For Diagnosis	For Cure of Localized Tumor	For Cure of Localized Inflammatory Disease	Would Not Operate	For Diagnosis	For Cure of Localized Tumor	For Cure of Localized Inflammatory Disease	Would Not Operate	For Diagnosis	For Cure of Localized Tumor	For Cure of Localized Inflammatory Disease
Histoplasmoma (2)												
H1	1	4	–	–	1	4	–	–	3	2	–	–
H2	–	5	–	–	2	2	1	–	2	3	–	–
	1	9	–	–	3	6	1	–	5	5	–	–
Chronic Focal Pneumonitis (6)												
P1	2	3	–	–	–	4	1	–	1	3	1	–
P2	4	1	–	–	3	1	1	–	4	1	–	–
P3	4	1	–	–	3	2	–	–	5	–	–	–
P4	4	1	–	–	3	2	–	–	5	–	–	–
P5	3	2	–	–	3	2	–	–	3	2	–	–
P6	2	3	–	–	1	2	2	–	3	1	1	–
	19	11	–	–	13	13	4	–	21	7	2	–
Hamartoma (5)												
H1	3	–	2	–	1	1	3	–	1	–	4	–
H2	1	2	2	–	–	1	4	–	1	–	4	–
H3	2	2	1	–	2	2	1	–	2	3	–	–
H4	3	–	2	–	2	1	2	–	2	2	1	–
H5	1	4	–	–	–	5	–	–	–	3	2	–
	10	8	7	–	5	10	10	–	6	8	11	–
Malignancy (8)												
Bronchogenic Carcinoma (5)												
M1	–	1	4	–	–	–	5	–	–	1	4	–
M2	–	1	4	–	2	1	2	–	3	1	1	–
M3	–	1	4	–	1	1	3	–	2	1	2	–
M4	–	2	3	–	4	1	–	–	3	1	1	–
M5	–	–	5	–	–	–	5	–	–	–	5	–
Alveolar Cell Carcinoma (3)												
M6	–	1	4	–	–	–	5	–	–	–	5	–
M7	1	1	3	–	–	3	2	–	2	1	2	–
M8	3	–	2	–	1	2	2	–	4	1	–	–
	4	7	29	–	8	8	24	–	14	6	20	–

For these reasons it is concluded that the view of many specialists in the field that accurate preoperative diagnosis is not possible is incorrect. Therefore, the doctrine of surgically exploring all such patients for diagnosis is not valid. If the proven diagnostic ability of a medical-surgical-radiologic chest conference is used as a basis for surgical exploration, in only a very rare malignancy will surgery not be performed, and 90 per cent of the patients with benign lesions will be spared the inherent morbidity and possible serious and permanent morbidity or mortality of thoracotomy. The reviewers of this series agree almost unanimously that "for cure of localized inflammatory disease" is not a valid reason for thoracotomy. The above recommended approach offers surgery to all who need it and few others are subjected. The exact details of the composition and criteria of such a medical-surgical-radiologic chest conference must be worked out in each individual hospital, but the data and suggestions in this paper are adequate guide lines.

In this series 50 consecutive patients with solitary pulmonary nodules or "coin lesions" had thoracotomies. If the recommended *more than two-thirds* criterion had been adopted, only 11 thoracotomies would have been performed; this would have included all 8 cases of malignant lesions, and 3 cases of hamartomas. The remaining 37 patients with inflammatory lesions and 2 with hamartomas would have been spared the morbidity and expense of thoracic surgical exploration. Even using unanimous agreement on nonmalignancy as a criterion, 19 of these patients would have been spared thoracotomy.

With all of the modern pressures for early definitive diagnosis and early surgery in cancer, some may argue the need for thoracotomy and histologic diagnosis in all cases, but, with a high degree of preoperative diagnostic precision, watchful expectancy appears to be indicated, as in many other types of lesions. If a rare malignancy is not operated on as early as it might have been due to an error in initial preoperative diagnosis by a properly qualified medical-surgical-radiologic chest conference, this is felt to be offset by the sparing of a very large group of patients from thoracotomy with its inherent morbidity, and its occasionally severe and permanent morbidity or mortality. It may also be pointed out that the prognosis of pulmonary malignancy is very poor, even with early surgery. In this series only 2 of the 8 patients with malignancy are alive and well 40 to 60 months postoperatively. Four are dead, and the other 2 are terminal with widespread metastatic disease. These patients were all operated relatively "early," as their lesions still fulfilled the authors' criteria for a "coin lesion." Every effort must be made to perform early resection of all malignancies, but not to the point of exposing large numbers of other patients to the hazards of anesthesia and major surgery.

It is interesting to compare the data in Tables VI, VIII, and IX. The same group of doctors shows a high degree of preoperative diagnostic ability concerning the malignancy or nonmalignancy of solitary pulmonary nodules, but, when asked if thoracotomy were indicated, they recommended surgical removal for diagnostic purposes. The surgeons' very high selection rate for thoracotomy is probably related to their training and the prevailing surgical doctrine of early surgical resection of all possibly malignant lesions. They are thoroughly familiar with the techniques, but they tend to minimize the admittedly small morbidity in all cases, and the rare serious morbidity and mortality. The selection of 32 of the 42 patients with benign lesions for thoracotomy by the surgeons seems extraordinarily high since only 3 of these patients were diagnosed as having malignancies by the majority of this same group. The almost unanimous opinion of the radiologists for thoracotomy in the malignancies correlates with their high degree of preoperative diagnosis of the malignancies. In spite of the correct diagnosis of *all* 42

benign lesions by the *majority* of the radiologists, they still recommended 16 for thoracotomy. The internists were still more conservative in recommending thoracotomy, choosing only 12 patients with benign lesions; but they failed to recommend 3 of the patients with malignancies for surgery. The radiologists thus demonstrate a notably greater ability to diagnose and recommend appropriate treatment for this group of patients than either the surgeons or internists. These data indicate that these physicians are not aware of their ability to correctly diagnose these lesions and lack confidence in this ability. It is therefore important that a medical-surgical-radiologic chest conference base its opinions and decisions on the members' diagnoses of malignancy or nonmalignancy rather than on the individual decisions for or against surgery. Various patient factors in individual cases, of course, will sometimes alter the course of action based on such a decision. According to the data in Table IX, the only acceptable indication for surgery, except in unusual cases, is for cure of localized tumor—usually reflected as "for diagnosis." Surgery for cure of localized inflammatory disease is rarely if ever indicated.

These data demonstrate a high degree of preoperative diagnostic accuracy of solitary lung lesions on the basis of the moderately complete preoperative protocols submitted. The additional data requested in many of the cases would serve to increase this accuracy, and such data should be available on request to any functioning clinical medical-surgical-radiologic chest conference. The extreme importance of complete clinical studies and thorough clinical and roentgenologic follow-up of *all* cases cannot be overemphasized, especially if the patient does not have surgery.

SUMMARY

An analysis of 52 consecutive surgically removed solitary pulmonary nodules, or "coin lesions," reveals the following:

1. The incidence of malignancy is 15.4 per cent. The most common pathologic entity is the granuloma (61.5 per cent) which includes the tuberculoma, coccidioma, histoplasmoma, and granuloma of undetermined etiology. Areas of chronic focal pneumonitis comprise 11.5 per cent, and hamartomas 11.5 per cent.

2. Pulmonary symptoms were present in only 3 patients, all of whom proved to have carcinoma.

3. Skin tests for tuberculosis, histoplasmosis and coccidioidomycosis were useful but not diagnostic.

4. Bronchoscopic examination was revealing in only 1 of the 7 patients proven to have carcinoma, and was negative in 8 patients with benign lesions.

5. Bronchial washings were negative for malignant cells in the 7 patients with malignancy; cultural studies were negative in 11 patients with inflammatory lesions including 1 patient with a tuberculoma showing acid-fast bacilli.

6. Surgical mortality was zero; major complications occurred in 4 patients (7.7 per cent), others suffered moderate complications, and all suffered the inherent morbidity and loss of time from thoracotomy.

7. Errors in medical-surgical-radiologic case management leading to thoracotomy or possibly contributing to the progression of pulmonary malignancy prior to surgery are discussed.

Preoperative clinical protocols and chest roentgenograms of 50 of these patients, along with a questionnaire, were submitted for review to a group of 15 specialists (5 internists specializing in diseases of the chest, 5 surgeons, and 5 radiologists) and revealed the following results:

1. There was marked variation of opinion as to whether the lesions represented "coin lesions," indicating the lack of specific meaning of the term and that it should not be used unless it is clearly defined.

2. The correct preoperative diagnosis as to malignancy versus nonmalignancy was made by the *majority* of the radiologists

in all 50 cases, while the *majority* of the surgeons misdiagnosed 5 and the internists 6. All of these 11 errors occurred among the cases of hamartomas and malignant lesions, with the exception of 1 granuloma which was called malignant by the surgeons.

3. No malignant lesion was erroneously diagnosed if *more than two-thirds* (11 out of 15) of the reviewers agreed that it was nonmalignant, and more than two-thirds did agree that all 37 of the inflammatory lesions and 2 of the 5 hamartomas were benign. Using this as a criterion for surgery, 39 of the 42 patients with nonmalignant lesions would have been spared thoracotomy. All 8 cases of malignant lesions and 3 cases of hamartoma would have been operated on because *more than two-thirds* did not agree that the lesion was benign. Statistical analysis shows that with a 6 member medical-surgical-radiologic chest conference less than 1 per cent of cases presenting malignancies would not be operated on if *more than two-thirds* (5 or more) agreed that the lesion was benign and that only 10 per cent of the patients with benign lesions would be subjected to thoracotomy, mostly patients with hamartomas.

4. Surgical intervention, independent of the stated preoperative diagnostic impression by the *majority* of the reviewers, was recommended in 64 per cent (32 out of 50) of the cases. The *majority* of the radiologists recommended surgery in 46 per cent of the cases, the *majority* of the surgeons in 78 per cent, and the majority of the internists in 34 per cent. The marked discrepancy between this recommendation for surgery and the demonstrated diagnostic accuracy is apparently due to these physicians' unawareness of their diagnostic ability and their lack of confidence in it.

5. The reason listed for recommending surgical intervention was almost always "for diagnosis," except for some lesions preoperatively diagnosed as malignant when "for cure of localized tumor" was the reason stated. Removal "for cure of localized inflammatory disease" was almost never cited, and apparently was not considered an adequate indication.

Patients presenting with solitary pulmonary nodules, or "coin lesions," should be studied by a medical-surgical-radiologic chest conference, probably consisting of 2 specialists in each specialty. If 5 of the 6 (*more than two-thirds*) agree that the lesion is nonmalignant, exploratory thoracotomy should be withheld and the patient carefully followed. It even appears to be justified to withhold surgery if 4 of the 6 (*two-thirds or more*) agree that the lesion is nonmalignant. The exact constituency of such a chest conference and the precise criteria adopted must be modified to meet the local situation, but can be based on the statistical data from this series.

CONCLUSIONS

The concept of a thorough clinical evaluation of patients with solitary pulmonary nodules, or "coin lesions," followed by exploratory thoracotomy on *only* the relatively few selected cases on whom *more than two-thirds* of the members of medical-surgical-radiologic chest conference *do not agree that the lesion is nonmalignant* has been presented. Most of these patients will have malignancies and most of the remainder will have hamartomas. The majority of inflammatory "coin lesions" will be called unequivocally nonmalignant by such a chest conference. Most of the preoperative diagnoses are clear-cut from such a conference and routine surgical exploration appears unwarranted; exploration for the purpose of diagnosis has a very limited role. On a statistical basis more than 99 per cent of the malignancies will be operated on and only about 10 per cent of the patients with benign lesions will be subjected to thoracotomy if the above criterion is used with a 6 member chest conference. In this series, if this criterion had been followed all of the cases of malignant lesions, some hamartomas, and *none* of the in-

flammatory lesions would have been operated on.

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LAMINAGRAPHIC OBSERVATIONS OF THE LUNG VASCULATURE IN CHRONIC PULMONARY EMPHYSEMA*

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THE increased incidence of chronic pulmonary emphysema has stimulated considerable physiologic investigation which has led to a better understanding of the altered physiology. Still, there remain important unanswered questions, namely: diagnosis of its very early stages by a comparatively simple routine procedure, the assessment of anatomic damage, and the clarification of the basic physiopathogenesis.

The clinical ancillary methods of diagnosis and prognosis in this disease have been but slightly improved. Conventional roentgenologic methods have proven to be unreliable in the diagnosis of different variants of emphysema[28,48] and especially in the detection of the early stages when the anatomic destruction starts to take place.[22]

The roentgenologic diagnosis of chronic pulmonary emphysema is still entertained on the basis of increased radiolucency and/or trapping in expiration especially when the diaphragmatic domes are flattened out. This will prove to be accurate and helpful in many cases; nevertheless, this simplified approach does not differentiate obstructive emphysema from other conditions that also produce hyperradiance, *e.g.*, severe bronchial asthma without destructive emphysema, simple over-inflation (senile, compensatory, or the thin-chested normals). Furthermore, the conventional criteria will not suffice to detect smaller local emphysematous areas when widely scattered throughout the lung,[22] mild emphysema complicating fibrosis and the centrilobular type of emphysema when any of these do not greatly disturb the diaphragmatic motion.

Finally, this approach will not provide judgement of the respiratory and hemodynamic derangements. The former has been approached in the past mostly in terms of quantitation of total lung volume which bears no direct relationship to the severity of emphysema.[10] A correlation of function to roentgenologic alterations in emphysema has been attempted by Barden and Comroe.[4] The hemodynamic abnormalities have been mentioned in the literature by several investigators who noticed varied alterations in the roentgenologic vascular pattern of these patients.[21,31,39] A step further was to focus the attention on the abnormal peripheral pattern of this vasculature.[1,3] These studies were based on conventional chest roentgenograms where definition of peripheral vascular structures is difficult due to layer superimposition.[15] The laminagraphic approach to this problem was apparently introduced by Scott and Lionberger,[41] and later mentioned by others.[23,25,35] Recently in an excellent paper, Fraser and Bates[20] took another step forward and described the different peripheral vascular patterns[9] in asthma and emphysema, concluding that laminagraphy is a valuable adjunct for the differential diagnosis. They emphasized the extreme tapering of the arterial tree at the level beyond the third and fourth branches in cases of emphysema.

These estimates of the vasculature in emphysema are still insufficient and do not explain most of the hemodynamic changes

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observed in emphysema. We are still lacking the proper roentgenologic signs to identify pulmonary hypertension before the clinical onset of cor pulmonale. This could be accomplished by the study of correlative data obtained by cardiac catheterization and laminagraphy.

The purpose of this paper is to add some descriptive observations to the present roentgenologic knowledge of the vascular derangement in emphysema. These observations will also be partially related to some qualitative changes observed in the pulmonary function studies.

MATERIAL AND METHODS

We have studied 17 patients with different clinical and physiologic degrees of chronic pulmonary emphysema. All of them, but one, were males. In most of them, the disease was moderate-to-far advanced as judged by the degree of steady effort dyspnea and clinical evidence of cor pulmonale. Table I lists the clinical and physiologic profile of the group. None of the patients were in overt failure at the time of the study, though several were receiving maintenance doses of digitalis. The physiologic determinations and laminagraphy were performed at close intervals.

I. PHYSIOLOGIC STUDIES

Pulmonary function studies (Table I) were performed according to established principles. The maximal breathing capacity was determined with a large spirometer and calculated from the volume expired in the first three-fourths of a second, multiplied by 40.[27] The distribution of inspired air was measured by the percentage of nitrogen expelled by the patient in forceful expiration at the end of an oxygen washout after he had reached an expired nitrogen concentration of 1 per cent (E.E.N.). The functional residual capacity (F.R.C.) was determined by a closed circuit helium technique.[34] Arterial oxygen and carbon dioxide determinations were performed with a Van Slyke apparatus and the pH was measured by using a Cambridge glass electrode and the results were corrected to 37° C. The pCO_2 was then calculated.[44] Expired gas was collected in a Douglas bag and analyzed with a Scholander apparatus. Physiologic dead space and ratio of dead space ventilation to tidal volume were then calculated. Mechanics of breathing were performed in the conventional way.[2] We do not have data on the patient's diffusion capacity of the lung, nor have we calculated the percentage of venous admixture.

TABLE I

CLINICAL-PHYSIOLOGIC PROFILE

Case No.	Age	Clinical Severity	Cor Pulmonale (compensated on digitalis)	M B C L./min.	End Expiration N_2	RV / TCL × 100	Phys. D.S. ml.	V_D / V_T × 100	Mean Expiratory Resistance cm./L./sec.	S_aO_2 per cent	$paCO_2$ mm. Hg
1	61	++++	*	19	4	78	396	68	21.02	87.76	44
2	64	++++	*	24	4	72	294	79	—	82.30	59
3	54	++++	*	22	3	—	300	72	26.24	86.10	52
4	63	++++	*	25	4.5	66	290	66	22.51	73.83	61
5	69	++++	*	25	5.5	—	298	69	—	81.36	60
6	62	++++	*	24	2	62	367	66	12.00	84.02	53
7	58	+++		20	—	—	358	68	15.58	89.67	44
8	54	+++		25	—	61	301	67	9.84	88.21	47
9	56	+++	*	24	5	62	222	65	18.50	85.47	55
10	61	+++		25	3.5	—	211	57	9.24	87.48	42
11	62	+++		28	3.5	—	—	—	—	—	—
12	61	++/+++		34	3	59	280	53	—	91.52	44
13	58	++		54	3.5	—	—	—	—	—	—
14	60	++		35	2	60	250	62	7.00	94.33	46
15	39	+/++		39	3	—	—	—	—	—	—
16	54	+		45	2	—	—	—	—	—	—
17	48	+		52	2.5	—	—	—	—	—	—

II. ROENTGENOLOGIC STUDIES

The fluoroscopic examination preceded all the other roentgenologic examinations. The diagnosis of emphysema was made in accordance with established principles and we concentrated mainly on the detection of areas of constant or increased radiolucency throughout the respiratory cycle, mediastinal displacements, and decreased diaphragmatic motion. Next, we obtained roentgenograms in the posteroanterior projections taken in deep inspiration and expiration. A lateral roentgenogram in deep inspiration was also obtained. We looked especially for evidence of air trapping, bullae, and extent of diaphragmatic motion. Special attention was given to the pattern of the blood vessels, their size, distribution, and the presence of peripheral areas of radiolucency.

LAMINAGRAPHIC STUDIES

A Picker 200 ma. machine was used. For the laminagraphic studies, we employed 50 ma. and a small spot focus. The kilovoltage was adjusted according to the size of the patient. The exposure time was always 3 seconds. We have used horizontal laminagraphy with a displacement range of 14 inches. At the beginning of the study, we compared individual vessel size, taking the laminagrams in the upright and horizontal positions. As no detectable change was found, we continued thereafter with the horizontal position in all the patients.

In most of the cases, we used the simultaneous multiple laminagraphic technique in a single exposure. This technique, described by de Abreu,[12] yields 7 laminagraphic layers per single exposure, each cut located 1 cm. apart. Thus, each single exposure will allow the laminagraphic study of 7 cm. of lung parenchyma in a given projection. A slight disadvantage is the presence of minimal blurring which reduces somewhat the sharpness of the picture. The advantages of reducing exposure to the patient while performing a complete examination outweighs the disadvantages. Simmonnetti and Giganti[48] have combined this procedure with angiography. In most of the patients we obtained the laminagraphic studies in the anteroposterior as well as in the lateral projection.[32]

Previous observations,[15,35] the study of plastic casts of the pulmonary circulation,[6] and our angiographic observations of the pulmonary artery in cadavers led us to conclude that the arteries and veins run mainly in a sagittal plane in the greatest portion of their length, and that only a minor part of them runs in the frontal plain. In view of these findings, we decided to concentrate especially on the lateral laminagrams at the level of the paramediastinal areas as well as peripherally. Presently, we feel that a good study of the pulmonary vessels which will map out all pulmonary segments can be achieved by the simultaneous 7 layer laminagrams through 1 single exposure of both right and left lateral projections.

ADVANTAGES OF THE LATERAL LAMINAGRAM OVER THE ANTEROPOSTERIOR LAMINAGRAM IN THE STUDY OF EMPHYSEMA

The anteroposterior laminagram yields essentially a picture of superimposition of vessels within the upper and lower lung fields separated by a radiolucency at the level of the midlung field. In this projection, the vessels are shortened and the study of the periphery of the lung is partial, and probably represents one-third of the true peripheral lung field. Within this periphery, the background is hazy due to the increased secondary radiation emanating from the rib area (Fig. 1).

In the anteroposterior projection, the vessels of the right middle lobe and lingula, as well as the vessels of the superior segment of the right lower lobe, are only partially visualized and mostly seen end-on. The limits of the lobes cannot be delimited in this projection. This is especially true in the areas of the right costophrenic angle which do not belong to the right middle lobe, but to the anterior segment of the right lower lobe.



FIG. 1. Case 10. Anteroposterior laminagram, 12 cm. The size of the "hole" is increased and within it the vessels are small. The "hole" is delimited by V_2 above, and A_8 below which in this case is displaced downward. The horizontal fissure (F) is thickened. Note the extensive costal blurring. TA = truncus anterior.

The lateral projection affords a better visualization of the periphery, which is seen to a larger extent than in the anteroposterior projection. The study of the periphery of the lung requires more than just observing the areas adjacent to the costal wall and should include also the periphery of the individual lobes particularly within the midlung field. In the upper lobe when the vessels are involved in any pathologic process, the lateral laminagraphic projection will clearly identify the individual segments (Fig. 2).

Lateral laminagraphy is also superior for the individualization of the vessels of the inferior lingular segment and the vessels of the lower lobe: anterior basal segment (A_8 and V_8), the lateral basal segment (A_9 and V_9) and posterior basal segment (A_{10} and V_{10}) (Fig. 3 and 4). The artery and vein of the medial basal segment (A_7 and V_7) are very poorly seen on the anteroposterior laminagram due to superimposition with the shadow of the heart. In the left lung, the cardiac shadow also interfered with the laminagraphic visualization of A_{10} and V_{10}. In the anteroposterior laminagram, the veins of the upper lobe are shaped with the concavity toward the mediastinum while the arteries are conveyed in the same direction. In the lower lung field the reverse is true: the veins are convex and the arteries concave toward the mediastinum.

IDENTIFICATION OF THE VESSELS ON THE LATERAL LAMINAGRAM

Right Lung. The vessels of the right lung will be described first. The right main pulmonary artery cannot be clearly delimited. It appears as a somewhat rounded shadow, obscuring the anterior one-half of the trachea at the level of its bifurcation. Anteriorly, it cannot be separated from the superimposed shadow of the superior pulmonary vein (Fig. 4).

The right main pulmonary artery gives



FIG. 2. Case 9. Right lateral laminagram, 12 cm. Note the emphysematous area in the anterior (2) segment of the right upper lobe with abrupt end of dilated segmental vessels, while the posterior (3) and apical (1) segmental vessels are preserved. The confluence of the inferior pulmonary veins (I.V.) is clearly seen.

off an anterior superior branch, the truncus anterior (Fig. 1), which branches off into the anterior segment artery (A_2) and the apical segment artery (A_1) of the superior lobe (Fig. 4). The posterior segment artery (A_3) takes off directly from the pulmonary artery in its descending portion.[6] The veins accompany the arterial course and can be identified by a simple rule: when the bronchus runs horizontally, the artery is above it and the vein below it; when the bronchus runs perpendicularly to the diaphragm, the artery is posterior and the vein anterior to the bronchus (Fig. 4). A_2 and V_2 are vessels of greater caliber than the vessels supplying the apical and posterior segments of the upper lobe. A_2 is particularly well visualized, extending from the anterior aspect of the trachea up to the periphery. Its inferior branch is also well visualized. The vein (V_2) is well seen above and parallel to the horizontal fissure and can be followed up to its drainage into the superior pulmonary vein, just anteriorly to the pulmonary artery



Fig. 3. Case 7. Left lateral laminagram, 8.5 cm. Somewhat better preserved circulation than on right side (Fig. 11) but showing scattered destruction, more marked in segments 2, 3, 6, 7 and 8. The lateral "hole" is increased in size. Note that the lingular segmental branches (4 and 5) are well seen. LPA=left pulmonary artery; LMB=left main bronchus; SPV=superior pulmonary vein.

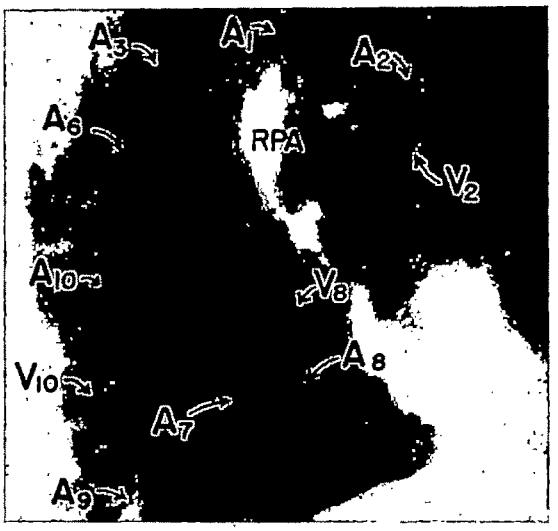


Fig. 4. Case 4. Right lateral laminagram, 13 cm. The vessels are large and well delineated. Their tapering off is smooth up to the segmental branches. There is a striking decrease in the number of subsegmental vessels and complete disappearance beyond. The cardiac output was actually low and the patient had pulmonary artery hypertension. The source of increased vascular resistance seems to be in the very peripheral arterial branches. Practically all the segments have decreased peripheral circulation but more so 2, 4, 5, 7 and 8. RPA=right pulmonary artery.

(Fig. 4). The apical segment arteries and veins (A_1 and V_1) are seen almost superimposed to the anterior aspect of the trachea. The peripheral branching of A_1 is poorly seen on the lateral laminagram because multiple structures at this level obscure it. The posterior segmental artery and vein (A_3 and V_3) run almost parallel and above the major fissure at about 3 cm. and 2 cm. of it, respectively.

At the level of the minor fissure, the descending pulmonary artery branches off anteriorly to supply the right middle lobe segmental arteries (A_4 and A_5) (Fig. 3). These two vessels emerge separately or as a single trunk which later subdivides.

The artery that supplies the lateral segment of the right middle lobe (A_4) emerges just below the minor fissure and is better seen in the peripheral lateral cuts (Fig. 3). The segmental artery and vein for the medial segment of the right middle lobe

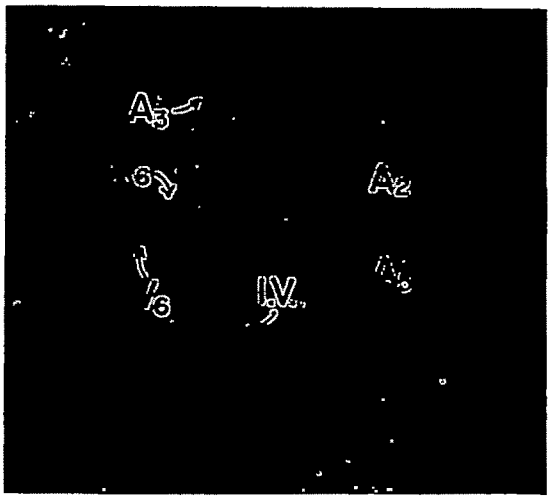


FIG. 5. Case 2. Right lateral laminagram, 11 cm. The vessels in the anterior segment of the upper lobe and lateral of middle lobe show abrupt decrease in size. The posterior segment of the upper lobe (3) and superior of inferior lobe (6) seem to have increased circulation. The confluence of the right inferior vein (I.V.) is well seen.

(A_5 and V_5) run parallel and above the major fissure. They are better seen in the medial lateral cuts. V_4 and V_5 can be usually followed up to the point where they drain into the superior pulmonary vein (Fig. 2). Occasionally, V_4 and V_5 drain into the inferior pulmonary vein.

The pulmonary artery, immediately below or at the same level of emergence of A_4 and A_5, gives off from its dorsal surface the vascular supply for the superior segment of the right lower lobe (A_6 and V_6) (Fig. 4). A_6 and V_6 run in a parallel fashion and almost perpendicular to the posterior wall of the thorax.

A_6 runs 2 to 3 cm. parallel and below the major fissure, and delimits with A_3 above the fissure a hyperradiant space of decreased vascularization that must not be confused with an emphysematous area. Next, the pulmonary artery branches off to supply the anterior basal (A_8), medial basal (A_7), lateral basal (A_9), and posterior basal (A_{10}) segmental arteries of the lower lobe, which are seen in that order from the front backward (Fig. 4).

On the lateral laminagram, the main inferior pulmonary vein is seen separated from the hilus by the right middle lobe bronchus close to its entrance to the left atrium (Fig. 5). It appears below the bronchus of the right middle lobe and the major fissure, and anterior to the bronchus for the right lower lobe.

Left Lung. On the lateral laminagram the left main pulmonary artery (LPA) is better visualized than the right. It is seen as a comma-shaped shadow encircling the left main bronchus (LMB) from above (Fig. 3). It gives off the artery for the anterior segment of the left upper lobe (A_2). V_2 runs parallel to it and drains into the superior pulmonary vein (SPV) which is located *below* the left main bronchus, thus being separated from the left main pulmonary artery (Fig. 3). The vessels that supply the apical portion of the apicoposterior segment A_1 and V_1 are seen in front and over the trachea respectively. The artery for the posterior portion of the apicoposterior segment of the upper lobe (called hereafter A_3 only for comparative purpose to the right side) branches out of the pulmonary artery in its most convex portion.[6] At this level of the left main pulmonary artery, V_3 runs almost perpendicular to it. This fact, plus its location below A_3, helps to differentiate V_3 from A_3.

The superior lingular segmental artery (A_4) and vein (V_4) run parallel, and are projected anteriorly (Fig. 3). A_3, V_3, A_4 and V_4 run in this order, from above downward in a horizontal and parallel fashion. The supply for the inferior segment of the lingula (A_5 and V_5) is two long branches that follow the aforementioned rule of the vein being placed below the artery and parallel to the major fissure. A_5 and V_5 are much more difficult to visualize than A_4 and V_4.

Below the major fissure, the left pulmonary artery branches off in a similar fashion to the right pulmonary artery.

ANTEROPOSTERIOR LAMINAGRAM

As stressed before, its main disadvantage lies in the difficulty to recognize the individual vessels; in particular, for the study of

emphysema, the lateral approach is far superior. Comprehensive descriptions of the vessels in the anteroposterior laminagrams have been published, and we will not dwell on this subject further.[23,35,39]

AREAS OF PHYSIOLOGIC HYPERRADIANCE

Certain areas in the lung are normally hyperradiant, not because they contain more air in absolute terms, but because the vessels are decreased in number and size. This represents indeed a diminution of the vessel's caliber. The reason for it is that these areas represent the juxtaposition of the periphery of 2 or more segments in the central core of the lung and at this level the vessels are obviously smaller. Several such areas are always present and should not be confused with emphysema.

There are 2 such areas in the midlung field best seen on the anteroposterior laminagram.

The anteroposterior medial cuts of the right lung show an ovoid area of radiance below A_2, the main axis of which is parallel to the minor fissure (Fig. 1 and 7). This area is limited below by the artery that supplies the anterior segment of the right lower lobe (A_8) or its vein (V_8). This radiolucency may be crossed in its middle portion by the artery or vein of the lateral segment of the right middle lobe (A_4, V_4). This same area of radiolucency is seen in the left lung 2 cm. to 3 cm. posterior to that visualized on the right side.

This area, within the left lung, is much more rounded than that on the right, and smaller and higher in relation to the opposite lung. These characteristics of the left-sided radiolucency are due to the fact that the left lung is smaller and the left pulmonary artery is higher than on the right side. In the left lung, A_3 and V_3 and A_8 and V_8 also limit the upper and lower margins respectively and the space is also crossed by A_4. These radiolucent areas, which we call anteroposterior physiologic "holes," are in fact the summation of the peripheral areas of several segments of the upper, middle, and lower lobe and have, therefore, vessels

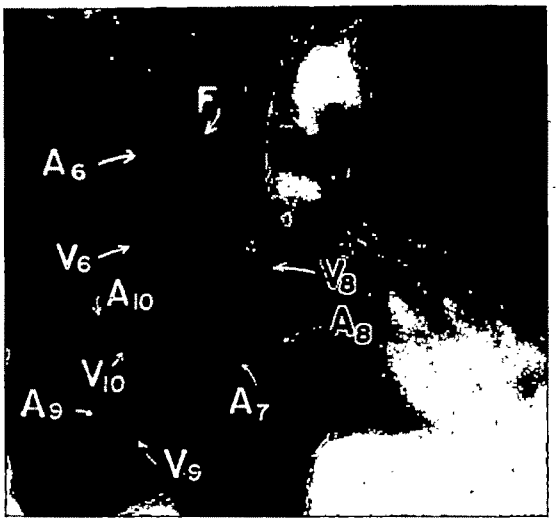


Fig. 6. Case 6. Right lateral laminagram, 9 cm. Decreased circulation in the lower lobe and relative increase in the middle lobe and posterior segment of the upper lobe (reverted pattern). The emphysematous areas in the lower lobe have displaced upward the long fissure (F). The lateral "hole" is increased.

of small size which accounts for the hyperradiance of these areas and their possible confusion with emphysema. Another area of normal hyperradiance is seen on the lateral laminagram and is also a source of confusion in cases of emphysema (Fig. 3 and 6). It has a triangular shape. The posterior border is formed by V_9, the anterior by the heart and inferior vena cava, its vertex by the descending pulmonary artery at the level where the inferior lobe segmental vessels take off and the base by the diaphragm. This radiolucency, which we shall call the lateral physiologic "hole," is usually crossed right in the middle by the medial basal segmental vessels (A_7 and V_7) and closer to the heart by the anterior basal segmental vessels (A_8 and V_8) (Fig. 6).

If true emphysema sets in in these particular areas of hyperradiance, it can be detected by the following: (a) the size of the "hole" is increased and its vessel's boundaries are pushed apart, and (b) the vessels normally traversing the "hole" (A_7, V_7, A_8, V_8) are either absent or decreased in size (Fig. 3).

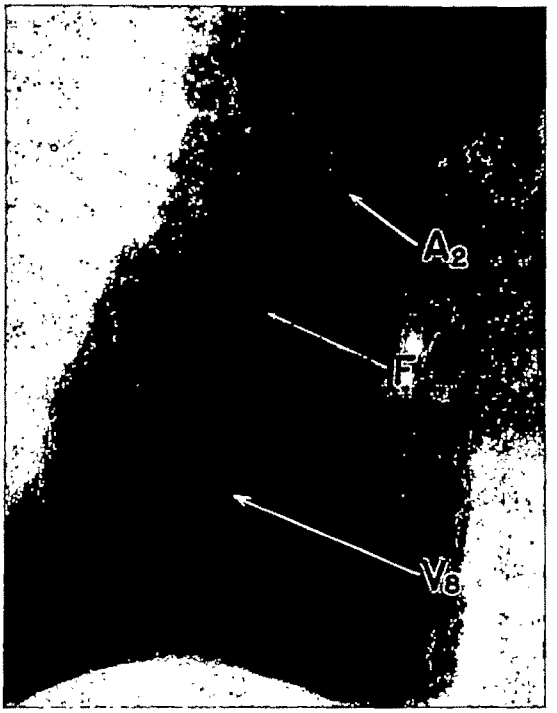


FIG. 7. Case 16. Anteroposterior laminagram, 17 cm. The physiologic right midlung "hole" is well seen delimited by A_2-V_2 and A_8-V_8 above and below the horizontal fissure (F). Note the costal blurring.

DIFFERENTIAL DIAGNOSIS OF "NODULAR" PATTERN

One of the greatest advantages of laminagraphy over plain roentgenography is the possibility of clarifying the nature of the diffuse nodular or "streaky" pattern, which is often seen in patients with chronic lung disease. These are a common source of roentgenologic confusion and are read, according to the radiologist's will, as either fibrosis, bronchovascular markings, peribronchial thickening, suspected bronchiectasis, etc. This is particularly a problem in the vicinity of emphysematous areas when the adjacent lung is compressed and its structures pushed together. In emphysema, laminagraphy will easily prove that in most cases they are blood vessels seen either end-on or as short discontinued strips. We use the following criteria to clarify this pattern: (a) the vessels seen "at length" will change their sizes at different laminagraphic layer depths while the fibrotic bands will not; (b) the suspected fibrotic shadows will not bear a topographic relationship to the vessel branching; and (c) circular shadows are clarified by studying the adjacent laminagrams distally and proximally. If the suspected shadow is a vessel, it will either increase or decrease in size. The fibrotic shadow will change at will and in many cases will appear as a hazy band (Fig. 8 and 9).

ROENTGENOLOGIC CRITERIA OF DIFFERENT TYPES OF EMPHYSEMA

1. BULLAE TYPE OF EMPHYSEMA

The bullae type is recognized on the plain chest roentgenogram by the absence of arteries and veins in a given area associated with a central radiolucency and surrounded by atelectatic lung. The anteroposterior laminagram usually gives a better visualization of this type of emphysema (Fig. 10).

2. DIFFUSE VESICULAR EMPHYSEMA

This emphysema is characterized mainly by diffuse irregular areas of air trapping, and may be detected during chest fluoroscopy and on the inspiration and expiration roentgenograms. On the anteroposterior laminagram, these areas are sometimes very difficult to detect and localize, espe-

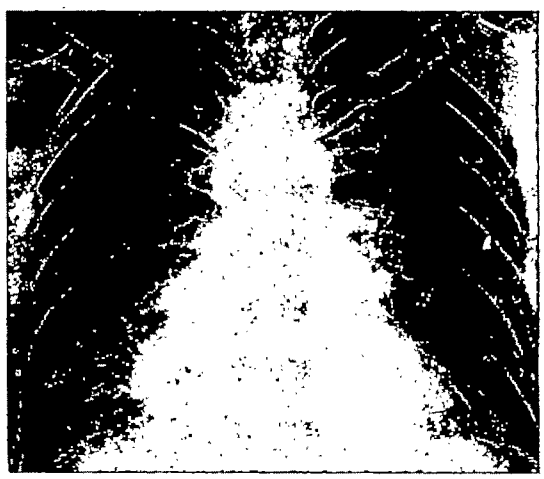


FIG. 8. Plain chest posteroanterior roentgenogram. Chronic diffuse interstitial fibrosis without evidence of emphysema.

cially when they are located peripherally or very centrally and particularly when they compromise selectively the posterior segment of the upper lobe, the middle lobe segments, or the superior segment of the lower lobe (Fig. 1 and 7). On the lateral laminagram, these areas will show absence or diminution of the vascularization peripherally and either normal (Fig. 3, 4 and 11) or dilated segmental vessels proximally (Fig. 2 and 5). In the detection of mild peripheral emphysema, we use an added technique. We obtain very peripheral lateral laminagraphic layers where the vessels of the fifth and sixth degrees are clearly seen as tiny round shadows, albeit, one cannot identify individual segmental arteries. The over-all number of these tiny shadows allows a comparative judgement of the over-all peripheral circulation in the individual segments previously identified (Fig. 3). Therefore, in this type of diffuse emphysema our criteria for detecting vascular abnormalities was: (1) over-all impression from fluoroscopy; (2) gross localization on the plain chest roentgenogram; (3) individualization of the involved segments on the lateral laminagram; (4) in the segments so individualized, we study the subsegmental vessels (fourth degree branching); (5) the study of the fifth and sixth degree of vessel branching was done on the very peripheral cuts to assess the over-all number of the small round end-on shadows representing the terminal roentgenographically visible vessels. The net result of the above-mentioned steps is shown in Table II. For comparative pur-



FIG. 9. Same case as in Figure 8. Right lateral laminagram, 11 cm. Unsuspected emphysematous areas in the anterior parts of upper and middle lobes were disclosed. The posterior segment of the upper lobe shows increased vascularization even when compared to the lower lobe vessels. The right middle lobe bronchus (B) is clearly underlined because of peribronchial fibrosis. The background is hazy because of the nodular type of fibrosis (N). Note that the nodules bear no topographic relationship to blood vessels.



FIG. 10. Case 3. Right lateral laminagram, 11 cm. Complete absence of peripheral vessels in the periphery of the upper lobe and marked decrease in number and size of the lobar and segmental vessels. Some of them have been reduced to barely threads traversing the big bullae. Note the crowding of the lower and middle lobe vessels displaced by the tension of the upper lobe bullae.



FIG. 11. Case 7. Right lateral laminagram, 9.5 cm. The vessels show very abnormal course. The size of them is strikingly diminished. The peripheral destruction is scattered. The lateral "hole" is increased. No areas with "compensatory" increased circulation are seen.

poses, we have numbered the segmental vessels identically in both right and left lung. The terminology is that of Jackson-Huber and Boyden.[6]

We did not attempt to quantitate the size of the vessels because of 2 main reasons: (a) the individual variations and (b) the impossibility of measuring the vessels always at the same level especially in the presence of anatomic destruction. This difficulty in quantitation also precluded the roentgenologic hemodynamic assessment. Therefore, we did not attempt to measure the degree of peripheral vascular resistance on the basis of the degree of segmental dilation located proximally to areas with decreased distal circulation. Emphysema located over the dorsal spine is harder to detect and will require usually laminagraphic oblique projections and more peripheral laminagraphic layers exposure.

3. EMPHYSEMA COMPLICATING FIBROSIS

When emphysema is suspected in a patient with marked scattered fibrosis, the criteria are more complicated since areas of compensatory overinflation produce radiolucencies which may or may not be areas with true emphysema (Fig. 8 and 9). Nodular fibrosis, especially when peribronchial, will present a perfect outline of the bronchi on laminagrams (Fig. 12).

4. CENTRILOBULAR TYPE OF EMPHYSEMA

There are, at present, no criteria for the roentgenologic detection of the centrilobular type of emphysema.

RESULTS

1. LOCATION OF DESTRUCTIVE AREAS

Table II shows that the peripheral vascular pattern is in most cases affected in a scattered fashion and involves multiple segments. Furthermore, the degree of segmental involvement varies in the same individual some times to a large extent. The apical segment of the upper lobes was in our

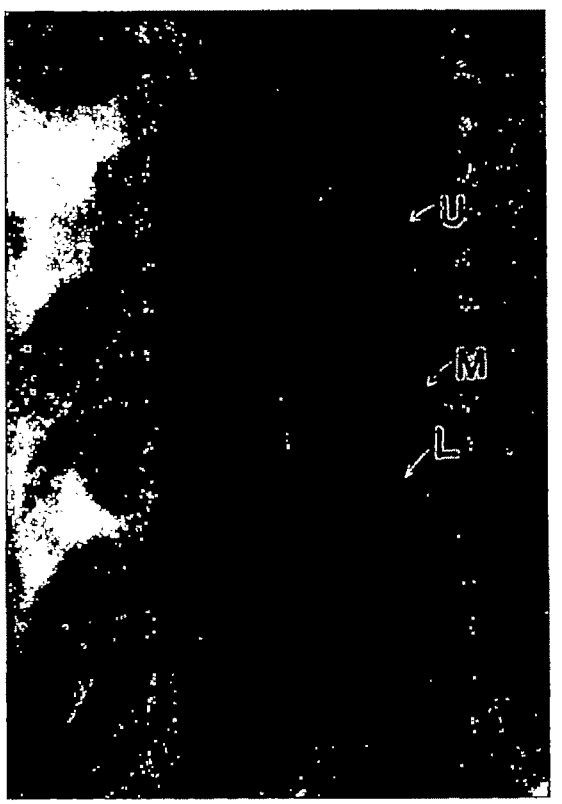


FIG. 12. Anteroposterior laminagram 10 cm. Advanced sarcoidosis. Practically all the bronchi can be visualized because of the underlying contrast supplied by the peribronchial fibrosis. Upper lobe (U), middle lobe (M) and lower lobe (L).

Table II

SEGMENTAL DISTRIBUTION OF DECREASED VASCULARITY*

Case No.	Right Lung Segments										Left Lung Segments*									
	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
1			+		++	++	++	++	++	++			++			++	++	++	+	+
2	+++	+		+	+				+	+			++	++	++	++	++		+	+
3	+++	+++	+++	+	+						+++	+++	+++	+	+					
4		++	+	++	++	++	+	+				++	+	++	++	++	+	+		
5	+++	+++					++	+									++	+	+	+
6						++	++	++	+	+			+				++	++	++	++
7	++	++	++	++		++	++	++					++			++	++	++	+	
8		++	++				+	+				+	+	++	++		+	+	+	+
9		++		++	++	+	+		+	+	+		+	+	+					
10		+		+	+	+			+	+					+				+	
11		+		+	+							+		+	+		+	+	+	
12							+	+						++	++		+			
13	++	+++		+++	+++						+++		+++		+				++	+++
14	+	+			+							+							+	+
15		++	+++	++	++		+	+				++	+	+	+					
16				+		+	+	+	+	+										
17																+			+	+

+ = mild; ++ = moderate; +++ = marked decrease in vasculature.
* For comparative purposes, we have assumed the same segmental distribution in both lungs.

series involved on fewer occasions than the rest. However, there was an obvious predilection for large bullae to be located in the upper lobe in which case the apical segment was not spared (Fig. 10).

Decreased vascularity of the posterior segment of the upper lobe, the medial and lingular lobe segments and the apical segment of the lower lobe were very hard to assess on anteroposterior laminagrams, but were clearly defined on the lateral laminagram (Fig. 2, 3, 4, 5, 6 and 9).

2. CHARACTERISTICS OF THE VESSELS IN THE AFFECTED AREAS

The ideal criteria would be the assessment of the smaller peripheral branches beyond the sixth order degree. Roentgenologically, this is next to impossible and of highly subjective nature. In our assessment, we have confirmed previous observations of abnormalities in vessel branching, splaying of the vessels and the presence of abnormal angles of bifurcation[4] (Fig. 11); the presence of increased radiolucency beyond these changes and the marked decrease in vessel size at the level beyond the fourth degree branching[20] (Fig. 3, 4, and 5). An added finding is the abnormal configuration of some vessels which are seen as discontinued tape-like shadows and are probably the expression of a tortuous course (Fig. 11). This roentgenologic feature of the peripheral blood vessels has been mentioned previously in the assessment of the vascular pattern in mitral stenosis and seems to be related to long-standing increased pulmonary vascular resistance.[15]

Helpful additional criteria of the subsegmental and more peripheral vessel abnormalities were obtained by observing the behavior of the segmental vessels. These might show: (a) abnormal engorgement localized only in the segmental branches, the periphery of which is affected by increased resistance on account of peripheral anatomic narrowing of the vascular bed (Fig. 5), and (b) the segmental vessels of the destructed peripheral areas may be of normal size, but there is a decrease in the subsegmental number of branches (Fig. 6 and 11).

3. REDISTRIBUTION OF THE BLOOD FILLING PATTERN

Most of the patients, regardless of the extent and location of the destructive process, maintained the normal relationship of the blood filling pattern; namely, increased sized vessels in the lower lobes in relation to the upper and middle lobe. In this sense, the hemodynamic disturbance of emphysema fits into the known pattern of other diseases exhibiting increased precapillary resistance. As known, this relationship is altered in the postcapillary resistance syndrome best characterized by mitral stenosis.[15,42] In only 2 of our patients, this relationship was altered and the vascularization of the upper lobes was larger than that of the lower lobes (Cases 1 and 6; Fig. 6). This brings up a very intriguing question. Do we really have "compensatory" redistribution of the circulation within the lung in cases of destructive emphysema? Laminagraphically, we can only say that it seems to happen in some cases. In a recent paper by West *et al.*,[47] regional blood flow variations within the lungs of patients with pulmonary diseases were described. They found striking increases in local blood flows in the apparently normal areas when there was disease involving the circulation elsewhere in the lung. Their method of measuring regional blood flows (radioactive carbon dioxide) correlated well with the angiographic studies done in some of their patients. We feel, therefore, that our laminagraphic findings may also point this out. Whenever present, the "compensation" is mainly seen within the affected lobe or in the very adjacent areas (Fig. 5 and 6). In none of the cases was a "compensatory" increase of vascularization noted over the opposite lung. That would be roentgenologically detectable only in cases of giant unilateral bullae and provided that the contralateral lung blood supply is preserved.[8] Most of the cases of chronic pulmonary emphysema are of a diffuse and

bilateral nature and circulatory compensation, if present, will be affected in a scattered way.

4. PATTERN OF PULMONARY ARTERIAL HYPERTENSION

We obtained hemodynamic data in only one patient of this series. The accepted method of measuring the tapering off of the vessels as a roentgenologic criterion of pulmonary hypertension is not feasible in emphysema as it is in other types of pulmonary hypertension.[11,24,40] In emphysema, due to the diffuse and aberrant location of the areas of increased vascular resistance, there is no way of standardizing these measurements. As a matter of fact, one of our patients (Case 4, Fig. 4) in whom cardiac catheterization was done and who was found to have a moderate degree of pulmonary artery hypertension (52 mm. Hg systolic) did not show an abnormal tapering off of the vessels, but a widespread decrease in the number of subsegmental vessels (Fig. 4). Until we can compare more hemodynamic and laminagraphic data, this question cannot be answered.

5. PHYSIOLOGIC "HOLES" (SEE MATERIAL AND METHODS)

Increase in size of the physiologic hyperradiances on the anteroposterior and lateral laminagrams, especially when accompanied by a decrease in size of the vessels normally transversing the space, was occasionally a helpful additional sign of emphysema.

6. CHARACTERISTICS OF THE BACKGROUND

Two main conditions can affect it: the presence of associated fibrosis and diffuse vessel engorgement. The first is a more common occurrence, and was usually identified by the lack of topographic relationship to blood vessel branches. The second is unusual in emphysema unless there is concomitant involvement of the venous pulmonary circulation. In some other cases, considered to have pure pulmonary fibrosis by clinical, physiologic and plain chest roentgenographic conventional criteria, we were surprised to find evidence of scattered emphysematous areas on laminagrams (Fig. 8 and 9).

7. LAMINAGRAPHIC AND PHYSIOLOGIC CORRELATIONS

These proved to be very difficult essentially because the pulmonary function tests express the physiologic derangement in average values for the total lung performance, while laminagraphy assesses the disease in terms of local anatomic destruction. Nevertheless, there were certain common trends:

a. The clinically most severely ill patients had the largest degree of physiologic derangement by almost every criterion (Table I). The laminagraphic findings also showed the largest involvement in terms of numbers of segmental vessels implicated and the degree of vascular destruction within these segments (Table II). Since we completed the investigation, 4 of these patients have died (Cases 2, 3, 4 and 5).

b. We expected to find a good correlation between the degree of devascularization and the amount of measured dead space ventilation. Though all the cases had an increase in physiologic dead space and in the ratio of dead space/tidal ventilation, a quantitative relationship was impossible to establish.

c. There was an apparent better correlation with the degree of mean expiratory mechanical resistance. This increased resistance leads to extensive air trapping, as indirectly supported by the findings of increased amounts of residual nitrogen after oxygen washout. The increased resistance certainly contributes to the creation of larger areas of decreased vascularization.

DISCUSSION

The main purpose of this paper is to advance the descriptive roentgenologic interpretation of chronic pulmonaryemphysema in the hope that a more analytic appraisal might lead to a better clinical definition of the different types of emphysema.

A. From the *anatomic* point of view, laminagraphy can be relied upon to detect

the anatomic destruction produced by emphysema of the moderate to large bullous type. One may also diagnose scattered emphysema by visualization of small, but multiple, destructive areas which would have been otherwise missed on the plain chest roentgenogram. These are the patients who often complain of marked disability and have abnormal pulmonary function tests, but their roentgenograms are not indicative of emphysema.

At the present time, we are still unable to detect cases with the centrilobular type of emphysema, which is increasingly coming into focus and is considered to be very common in most men over the age of 50.[33]

In recent years, there have been reports of surgical attempts for the treatment of this disease.[7,26] While resections of single giant bullae have met with some success, plication or resection for widespread emphysema has not been generally accepted. In these procedures, the surgeon has been guided essentially by the macroscopic appearance at the time of thoracotomy. With the help of laminagraphy, a careful preoperative plan could be designed regarding the extent of the procedure and the topographic approach.

B. *Functionally*, the correlations derived from the laminagraphic findings at present are equivocal. One may certainly be confident that areas devoid of circulation represent the main source of increase in the physiologic dead space and decrease in effective alveolar ventilation. That still leaves open to question the functional capacity of the areas with preserved circulation; mainly, in terms of contribution to the venous admixture and to the over-all perfusion-ventilation imbalance.

An important and practical advantage of laminagraphy is the clarification of the meaning of the plain roentgenographic signs of so-called "bronchovascular markings," suspected "fibrosis," "bronchiectasis," etc. Our increased experience with the use of laminagraphy[15] has shown that, in emphysema, most of these "markings" are indeed crowded blood vessels pushed away from the affected areas, or local vessels abnormally engorged. Functionally, that means that in many cases these areas with "increased markings" are indeed the best areas function-wise—areas where gas exchange can take place. The functional severity seems to go along with the extent of anatomic damage. Laminagraphically, correlation between the extent of damage and the decrease in diffusing capacity of the lungs would probably yield a very close relationship.

Another functional anatomic consideration is related to the actual size of the destruction in the "bloodless" areas. It is conceivable that postmortem injection will disclose the existence of a larger number of preserved vessels than seen on laminagrams *in vivo*. This will be the subject of a later report. *In vivo*, it is possible that damaged areas will tend to shunt away their circulation toward the better ventilated areas, therefore, increasing the "roentgenologic" size of the antomic destruction. It would seem then that the roentgenologic criteria would give a more true estimate of function loss than the anatomic postmortem assessment.

The altered hemodynamics of emphysema fit into the category of increased precapillary resistance. If the analogy were true, its roentgenologic counterpart would be similar to the one described for other diseases with the same hemodynamic substratum, as some forms of congenital heart disease and primary pulmonary hypertension.[14,45,46] In emphysema, this interpretation is more difficult because of several reasons: (a) the degree of pulmonary hypertension is usually only mild or moderate and, therefore, the roentgenologic changes are difficult to assess; (b) the hypertension is of changing magnitude in the same patient, as influenced by the variations in hypoxia, hypercarbia, swings in intrathoracic pressure, etc.; (c) the precapillary resistance is altered unequally in different areas of the lung due to the usual aberrant scattering of the anatomic lesions; therefore, one cannot, as in the pulmonary

hypertension of congenital heart disease, attempt to measure it always in the same location; and (d) present roentgenologic methods cannot differentiate, by the vessel's size only, pulmonary blood flow from pulmonary blood volume. It is known that central blood volume is very difficult to assess in the presence of increased vascular resistance and involves the knowledge of many variables like transmural vascular pressure,[9] the pressure gradient from pulmonary artery to pulmonary veins, pulmonary arterial vasoconstriction or obliteration, etc.[13]

The lack of hemodynamic data in the present series is unfortunate and prevents the laminagraphic correlation in terms of vascular pressures and resistances. In view of that, we shall only attempt at this time to put forward several hypotheses, and expect their clarification by further work.

1. The scattered distribution of anatomic damage could explain the presence of only moderate increases in pulmonary artery pressures found in most of the patients with chronic pulmonary emphysema.[5,38] The known large capacity of the lung vascular bed in the preserved normal areas offers a substantial avenue to partly offset the increased resistance of the destroyed areas.

2. Under stress conditions like exercise, infection, and bronchoconstrictive episodes, the capacity of the remaining vascular area may not be enough to accommodate the increased cardiac output, and pulmonary artery hypertension can increase to a severe degree.[18] This, once again, focuses the discussion on the role of hypoxia in the development of pulmonary hypertension. Although it has been proven that hypoxia increases the pulmonary artery pressure,[17,19,36] its quantitative capacity to do so and to shunt blood away from the hypoxic areas is open to question.[29] Indeed, it is possible that hypoxia is as much a cause as a result of pulmonary artery hypertension. It has been shown that the creation of pulmonary hypertension in dogs elicited a drop in paO_2 in the wake of an increase in venous admixture and decrease of diffusion capacity.[16] Obviously then, the detection of the early stages of pulmonary hypertension by roentgenologic means is of considerable importance.

C. *Perfusion-ventilation imbalance* is a paramount feature of emphysema. It seems to be determined by several factors, among which increased vascular resistance, decreased diffusing capacity and poorly ventilated areas are foremost. A less-mentioned factor is the increased intrapulmonary pressure so often found in these patients. The increased intrapulmonary pressure could be a most important element, conditioning the ebb and flow of the pulmonary vascular resistance, pressure and pulmonary blood flow, and as a result the distribution of intrapulmonary blood flow, affecting the ventilation-perfusion relationship. Rahn[37] has shown that positive pressure breathing effects an increase in pulmonary artery pressure and vascular resistance, decrease in cardiac output, increase in dead space ventilation and creates large ventilation-perfusion ratios. Interestingly enough, this increased vascular resistance seems to be effected in the precapillary area and, therefore, the pulmonary venous pressure is maintained near its former level. A practical implication of this increased pulmonary artery-pulmonary vein gradient could be that the direction of the collateral blood flow is reversed and may then proceed from the bronchial azygos vein system toward the pulmonary vein, increasing the degree of venous admixture. These collaterals have been shown to be greatly expanded in emphysema.[30] Normally, they allow the blood to flow from the pulmonary vein to the azygos vein, but, with increased artery and right heart chamber pressure while the pulmonary vein pressure is maintained, the direction of flow in the collateral circulation may be reversed. In our series, the patients who had the largest degree of mean expiratory resistance also had the lowest arterial oxygen saturation which could be explained on the above-mentioned basis. In one (Case 4), the hemodynamic recorded picture

during heart catheterization supported this contention. He had the lowest arterial oxygen saturation (74 per cent), one of the highest mean expiratory resistance (22.51 cm., H_2O/L./sec.) and moderately high pulmonary artery and right heart pressures (52 mm. Hg, systolic). He had no classic roentgenologic pattern of pulmonary hypertension and his segmental vessels tapered off gently. But in this patient, practically all the branches beyond the fourth degree were strikingly diminished. We assume that the area of increased vascular resistance was quite peripheral and located in the small arterioles beyond the fifth and sixth degree branching. This resistance may not be roentgenologically detected by proximal segmental vessel dilatation, as is common in other cases of pulmonary hypertension. The pattern here is similar to the one described by Steiner[45] in hypertension of interventricular septal defects where the vessels taper off gently until they suddenly disappear in the very periphery.

SUMMARY

Laminagraphic studies were performed in 17 patients with clinical and physiologic evidence of chronic pulmonary emphysema. The study centered on the morphologic changes of the segmental and subsegmental pulmonary blood vessels. A technique obtaining 7 simultaneous lateral laminagrams, 1 cm. apart, was used.

The pattern for roentgenologic identification of the pulmonary vessels in the lateral laminagram is presented. The pathologic changes observed were as follows: a decrease in the number of blood vessels; reduction in the number of secondary branching; abnormal regional vessel crowding; signs of blood flow redistribution within the lung; signs of increased pulmonary vascular resistance unequally distributed throughout the lung; and finally massive disappearance of the peripheral circulation.

The importance of these findings as a preoperative guide and some of the physiologic-anatomic correlations in emphysema are discussed.

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INTERLOBULAR SEPTA THICKENING IN LIPID PNEUMONIA

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ROENTGENOGRAPHICALLY visible interlobular pulmonary septa, first described by Kerley[20] in 1951, are short linear shadows best seen above the costophrenic angles perpendicular to the lateral chest wall. They vary in spacing and range in width from barely visible to 2 mm.[7] They terminate at or close to the pleura, may extend several centimeters into lung parenchyma, and although most common at the bases may appear at any height along the chest wall. They are usually bilateral but may be unilateral.[12]

Gough[10,11] demonstrated that these lines (Kerley B lines) represent interlobular septa; these delineate the secondary lung lobules. The septa, which are more prominent at the periphery of the lung,[33] consist of pulmonary lymphatics and veins and loose connective tissue.[27]

It is now generally agreed that Kerley B lines may be produced by any process which thickens the septa or their contents. The conditions producing these septal lines may be divided into two major categories:

(1) *Distention and infiltration of lymphatics and connective tissue.* It is not clear if cellular infiltration of connective tissue, lymphatic obstruction, or both are necessary for the formation of roentgenographically visible interlobular septa. Grainger and Hearn[12,13,14] state that mediastinal lymphatic obstruction is the major factor, with interference of central lymph flow and distention of lymphatics. They mention mediastinal sarcoidosis, the reticuloses, lymphoma with hilar adenopathy, and possibly bronchiectasis as examples.

Although central lymphatic obstruction such as caused by ligation of the thoracic duct does produce elevated pressures in the lymphatic system distal to ligation, the pressure falls shortly with the opening of collateral lymphatic circulation.[29,23] This suggests that central lymphatic obstruction is not a major factor in the formation of Kerley B lines, but rather local lymphatic overload, obstruction, and cellular infiltration are of prime importance. This is supported by the fact that well studied cases with Kerley B lines and lymphangitic carcinomatosis or pneumoconiosis display their pathology mainly at a local rather than central level. It would appear that any disease process that affects the local pulmonary lymphatic system either directly (*e.g.*, lymphangitic spread of carcinoma[14,25] or lymphoma[14]), by overloading the macrophage-lymphatic drainage system (*e.g.*, the various pneumoconioses[20,32] or primary pulmonary hemosiderosis[14]), or by fibrous tissue proliferation with obstruction of lymphatics and infiltrating connective tissue (*i.e.* sarcoidosis[6]) may cause widening of the interlobular septa.

(2) *Increased pulmonary venous and capillary hydrostatic pressure* over 20–30 mm. Hg, thus exceeding the colloid osmotic pressure of the plasma.[2,12,24] Examples are mitral stenosis,[2,7,14,24] mitral insufficiency,[12] pulmonary venous occlusion,[14] anomalous pulmonary venous drainage into the portal system,[26] and, rarely, chronic left heart failure. In fact, Grainger[14] states that any condition which impairs clearance of pulmonary venous blood may cause Kerley B lines. Left-to-right shunts do not cause interlobular lymphatic dilatation since the pressure is high in the pulmonary arterial but not in the capillary system.

Grainger[13,14] postulates that increased capillary permeability which allows transudation of fluid into the septa (interstitial rather than alveolar edema) may cause

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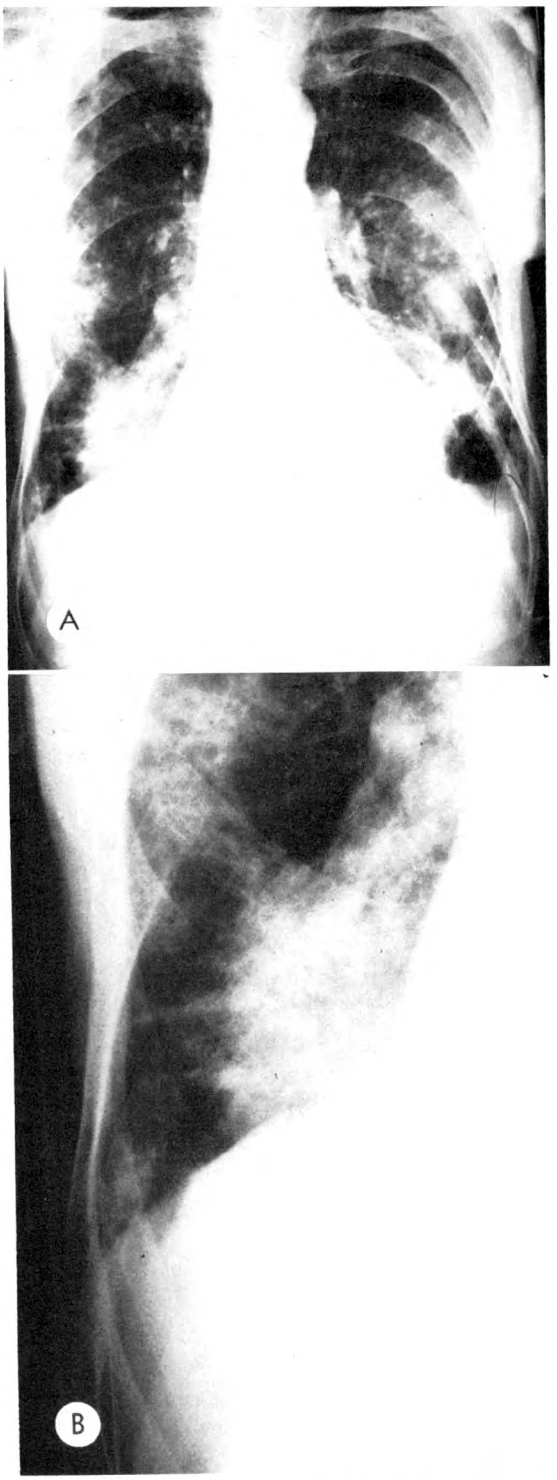


FIG. 1. Case 1. (*A*) Extensive bilateral lower lobe consolidation is present, more marked on the right. Kerley B lines are present bilaterally, more outstanding on the right. (*B*) Magnification of right lower hemithorax.

Kerley B lines. Examples suggested are hypersensitivity reactions to drugs and exposure to irritant gases. He also suggests that decreased colloid osmotic pressure, such as seen in hypoproteinemia, theoretically could cause Kerley B lines.[13] Dihlmann[5] states that Kerley B lines were present in 12.5 per cent of 64 patients with severe starvation and edema, but the cases are not well documented and total protein determinations done in only 2 patients were normal.

Since one of the predominant pathologic reactions in lipid pneumonia is thickening of interlobular septa by oil-filled macrophages and fibrosis, it would seem that this disease should cause visible septal lines on roentgenograms. A review of past cases with lipid pneumonia seen at Michael Reese Hospital uncovered 2 cases with visible basal interlobular septa. Recently 2 more patients having lipid pneumonia with Kerley B lines came to our attention. It is the purpose of the authors to report this finding and emphasize its importance in the diagnosis of lipid pneumonia, a disease that is being recognized with increasing frequency.

REPORT OF CASES

CASE 1. A.H., a 72 year old white male retired barber, was admitted to Michael Reese Hospital on January 27, 1958 because a chest roentgenogram (Fig. 1, *A* and *B*) showed dense zones of consolidation in the right middle and lower lobes, patchy left lower lobe consolidation and pulmonary emphysema. Prominent Kerley B lines were present in the right lung base.

His chief complaints were of cough productive of several teaspoonfuls daily of whitish sputum for many years and two-block exertional dyspnea. He denied wheezing, chest pain, or hemoptysis. He had been at another hospital in 1950 where bronchoscopy was performed, and he was told he had bronchiectasis of the right lung. Surgery was recommended but refused by the patient. The previous chest roentgenograms were not available for review. The patient stated that he took mineral oil daily for 10 to 15 years, often drinking it from the bottle. Physical examination revealed marked dorsal kyphosis.

The lungs were hyperresonant except for some dullness at the right lung base posteriorly. There were decreased breath sounds and coarse rales in this region. The purified protein derivative (PPD) #1 skin test was positive. Six sputum specimens were negative for acid-fast bacilli, and 4 were negative for malignant cells. Three specimens showed moderate amounts of fat droplets. He was started on antibiotic and bronchodilator therapy and discharged with the diagnosis of lipid pneumonia with superimposed infection.

He was readmitted on December 18, 1959 with progression of his cough and dyspnea, and at this time had pedal edema and hepatomegaly. An electrocardiogram now showed P-pulmonale. Arterial blood analysis revealed slight oxygen desaturation at rest and exercise with normal carbon dioxide tensions. Digitalis was added to his therapy and he was discharged with the additional diagnosis of cor pulmonale.

He was readmitted 2 weeks later with acute pulmonary edema and pneumonia and expired.

At autopsy the lungs together weighed 960 gm. The pleural surfaces were covered by fibrous tags. The right lung was firm and nodular, and contained several abscess cavities. Microscopic sections showed a diffuse interstitial fibrosis in the lungs. The right lower and middle lobes contained large amounts of lipid material, with scattered granulomas composed of epithelioid cells (Fig. 2). The final diagnosis was chronic diffuse fibrosing interstitial pneumonitis, lipid pneumonia of the right middle and lower lobes, and abscess of the right lower lobe.

Case II. P.H., an 85 year old white male bookkeeper, was admitted to Michael Reese Hospital on April 4, 1956 with a one day history of chest pain and weakness. Past history revealed exertional dyspnea and wheezing of 10 years' duration and productive cough of 6 months' duration. These symptoms were progressive in nature and he had lost 20 pounds in the several months preceding admission. No attempt was made to elicit a history of oil ingestion. The patient was moderately dyspneic at rest and had bilateral rhonchi and basilar rales. An electrocardiogram showed an atypical posterior wall myocardial infarction. Repeated sputum examinations for fungi and acid-fast bacilli were negative. Chest roentgenograms (Fig. 3, *A* and *B*) revealed moderate generalized cardiomegaly and aortic calcification. Dense zones of parenchymal infiltration were present in both lung bases, more prominently on the right. In addition, there were a number of fibronodular

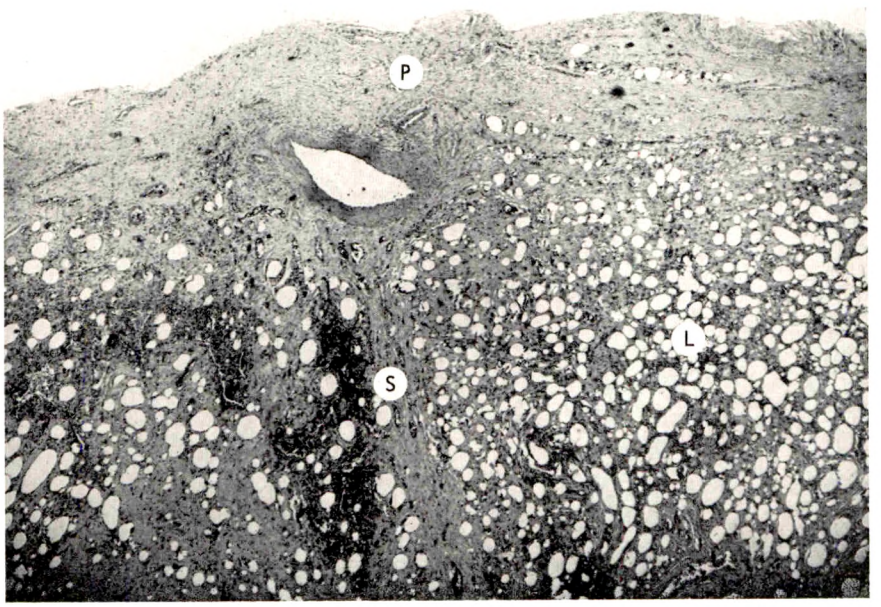


Fig. 2. Case 1. Low-power photomicrograph of right lower lobe autopsy section. P: thickened pleura, S: interlobular septum thickened by fibrosis, L: oil-laden alveoli with thickened alveolar walls (H & E stain, × 8).

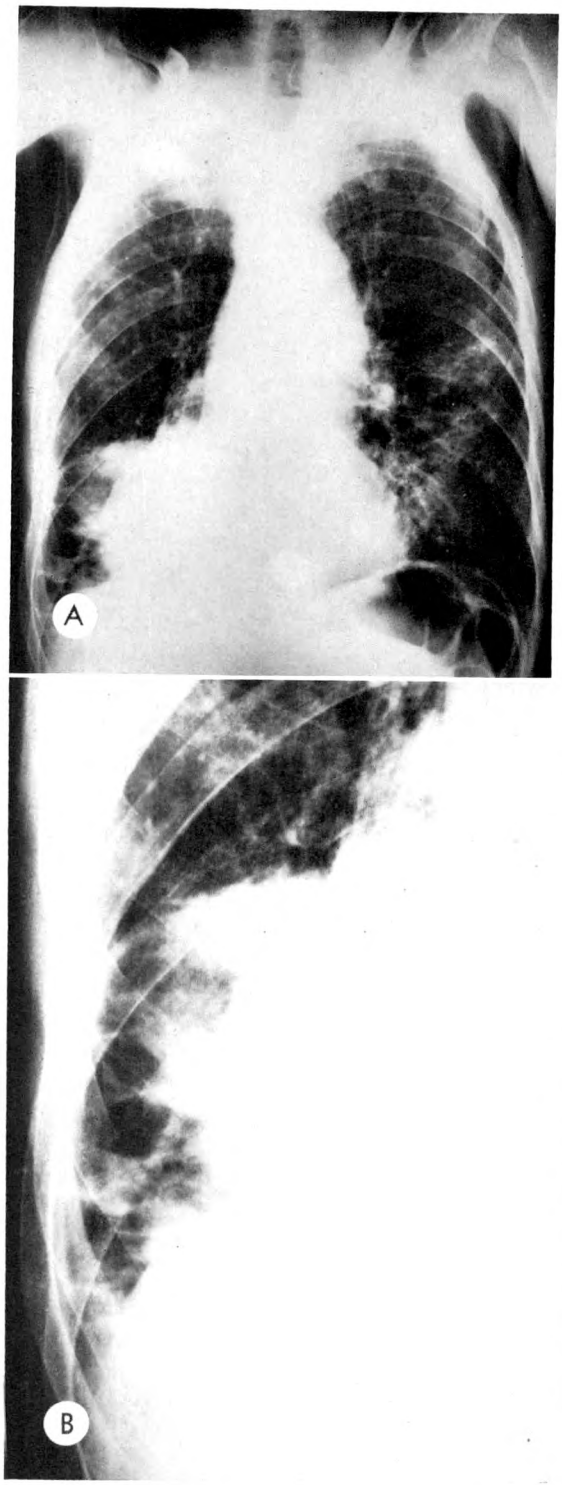


FIG. 3. Case II. (*A*) Dense parenchymal consolidation is present in both lower lobes, more marked on the right. On the original roentgenograms it was evident that the middle lobe was not involved. Prominent interlobular septa are present in the right lung base. (*B*) Magnification of right lower lung field.

shadows of varying size in the right upper lobe. In both lung bases, more prominent on the right, were numerous fine lines running transversely from the pleural surface for 1 to 5 cm. into the lung parenchyma (Kerley B lines). No pleural effusion was evident, nor was there any sign of mediastinal lymphadenopathy. About one month after admission the patient went into irreversible congestive heart failure and expired.

At autopsy the right lung weighed 950 gm., the left 750 gm. There was bilateral lower lobe distortion with multiple scars and lobulations. The cut surface was dry and granular and a few bronchiectatic cavities were seen in both lower lobes. The hilar lymph nodes were enlarged and firm. Microscopic examination showed the alveoli to be distended and filled with fine sudanophilic material. Some of the vacuolated alveolar spaces were lined with giant cells. The interstitial tissue was markedly thickened and contained numerous round cells. There was also infiltration along septal lines. The hilar lymph nodes and spleen contained large foamy cells and accumulations of giant cells. The anatomic diagnosis was bilateral organizing lipid pneumonia of lower lobes and severe coronary arteriosclerosis. There was also a small pulsion diverticulum of the esophagus.

CASE III. E.W., a 66 year old Negro male, former steelmill worker, was admitted to Michael Reese Hospital on December 23, 1960 because a survey chest roentgenogram (Fig. 4, *A* and *B*) revealed a large zone of relatively dense consolidation in the left lower lobe and some questionable infiltration in the right lower lobe. Thickening of interlobular septa was grossly evident in the left lung base. There was no pleural effusion or mediastinal lymphadenopathy. He had a past history of treated lues and exhibited luetic optic atrophy and saber shins. He also had a history of a chronic productive cough of one cup per day of whitish sputum, one- to two-flight exertional dyspnea, wheezing, and mild left pleuritic chest pain of many years' duration. There was no history of previous chest disease and a chest roentgenogram taken in 1939 at another hospital was reported as negative. This was not available for review. Additional complaints

included chronic constipation for which he had taken mineral oil for many years. Physical examination revealed good chest and diaphragmatic motion, decreased breath sounds and generalized crepitant and moist rales at both bases. Routine laboratory data including liver profile were normal except for a 2-plus Reiter's complement fixation test. An electrocardiogram was normal. Skin test with PPD intermediate strength was 5 mm., and with histoplasmin 1:100 8 mm., induration at 48 hours. Six sputums were negative for acid-fast bacilli and 3 heated aerosol sputums were negative for cytology. Four sputums (fasting state, low fat diet, after oral hygiene) revealed moderate amounts of fat droplets. Bronchoscopy was negative except for slight rigidity of the left lower lobe bronchus. Random biopsy of both lower lobe bronchi and right scalene lymph node biopsy were negative. The patient is being followed with the diagnosis of chronic bronchitis and lipid pneumonia.

Case iv. E.E., a 66 year old white male physician, was admitted to Michael Reese Hospital on October 26, 1961 because a chest roentgenogram (Fig. 5, *A* and *B*) revealed extensive pneumonia in the right middle and lower lobes. This had a homogeneous ground-glass appearance. Dilated interlobular septa were quite visible on the right side. In the left lung base, there was also an area of pneumonia though much smaller than on the right. The dilated septa associated with the left pneumonia were less distinct than on the opposite side but definitely present. There was no history of cough, dyspnea, wheezing, chest pain, or hemoptysis. The patient had noted some vague malaise and easy fatigability in the month prior to admission and had lost 5 pounds during this time. He had a long history of spastic colitis and diverticulosis for which he took 30 cc. of mineral oil nightly. Physical examination revealed a slight pectus excavatum, the chest was resonant throughout, and there was good diaphragmatic motion. There were a few subcrepitant rales at the right lung base. All laboratory data including viral and bacterial agglutinations and fungal complement fixations were normal. Skin tests with PPD #2 and histoplasmin 1:100 gave 10 mm. induration at 48 hours. Four 24 hour sputums were negative for acid-fast bacilli and 5 heated aerosol sputums were negative for cytology. Four

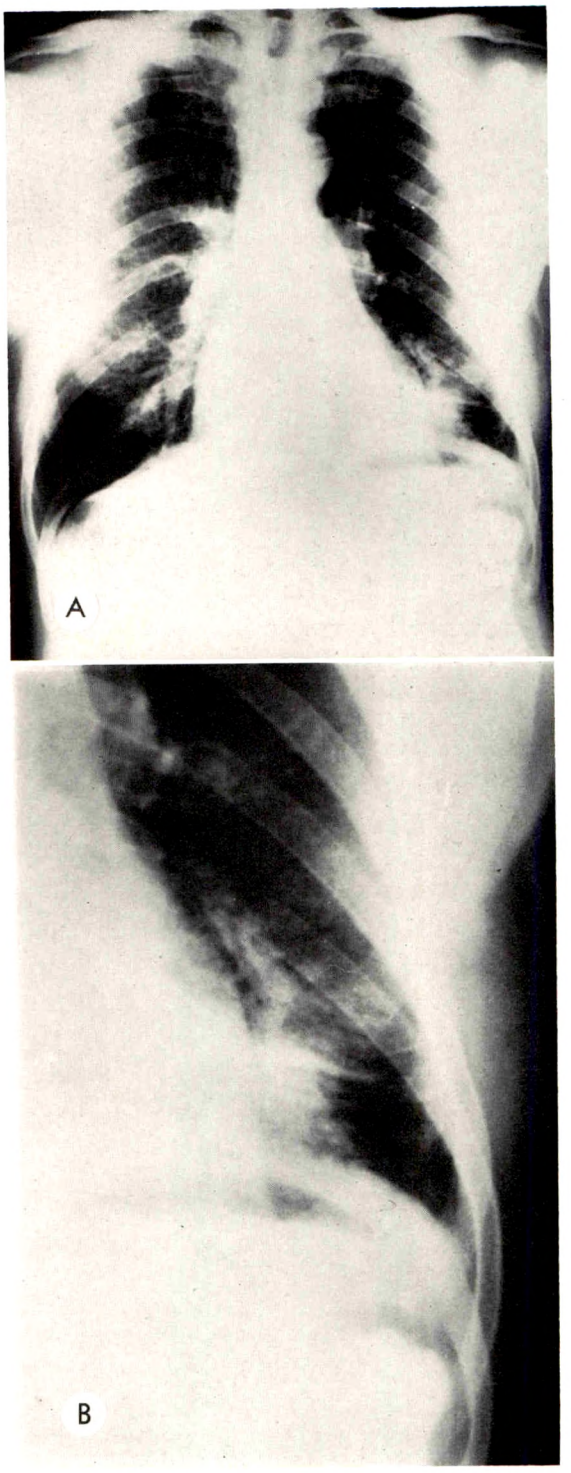


Fig. 4. Case iii. (*A*) Dense, well-circumscribed consolidation is present in the left lower lobe and possibly some right lower lobe infiltration of slight degree. Kerley B lines are prominent in the left base. (*B*) Magnification of left lower lung field.

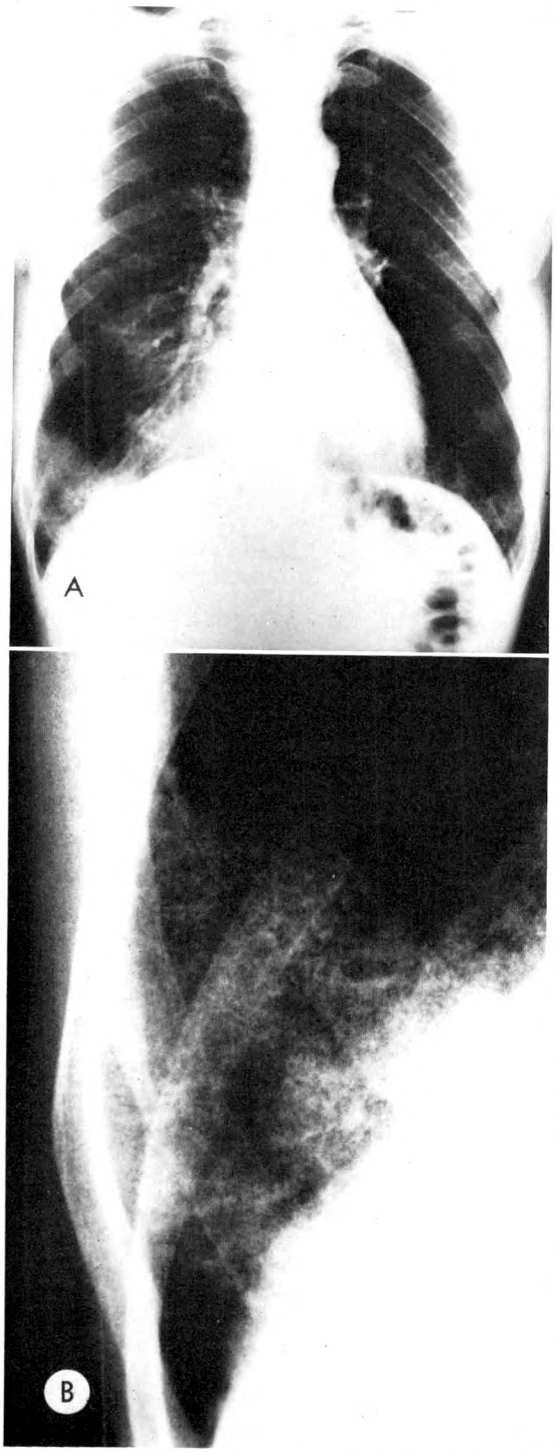


FIG. 5. Case IV. (*A*) Extensive homogeneous right lower lobe and right middle lobe consolidation is present. A smaller area of pneumonitis is present in the left base. Kerley B lines are present bilaterally. (*B*) Magnification of right lower lung field.

bronchial lavages and 2 sputums (fasting state, low fat diet, after oral hygiene) revealed moderate to marked amounts of fat droplets. Bronchoscopy showed moderate hyperemia of the right middle and lower lobe orifices and random biopsy on the right was negative. The patient is being observed with the clinical diagnosis of lipid pneumonia.

DISCUSSION

Lipid pneumonia was initially described only in debilitated infants,[22,29] but as interest in the disease grew it became evident that it was frequently found in the elderly and chronically ill.[19] Volk *et al.*[38] reported an incidence of 14.6 per cent in 389 chronically ill patients. It was recognized that neurologic diseases interfering with swallowing, palatal, and cough reflexes, and gastrointestinal disorders such as achalasia and esophageal diverticula predispose to chronic aspiration[8,9] and, if associated with mineral oil ingestion, to the development of lipid pneumonia. Schneider[35] in 1949 emphasized the occurrence of lipid pneumonia in otherwise healthy ambulatory adults and many cases are now first discovered on routine chest survey roentgenograms of the asymptomatic population.

There is no good explanation why some people develop lipid pneumonia with chronic mineral oil ingestion while the majority, even with predisposing factors, does not.[8] If detailed histories are taken in all cases, a large percentage will supply a reason for chronic aspiration. Autopsy in Case II revealed an esophageal diverticulum. Cases I and III had long histories of chronic bronchitis and, perhaps, as a result damaged bronchial defenses, but no reason for aspiration was apparent in these patients. The patient in Case IV after extensive questioning admitted that he took mineral oil plus a potent sedative at bedtime. Several authors have shown that oil introduced into the pharynx during sleep is capable of entering the bronchial tree without exciting reflex inhibition.[30,31]

If aspiration does occur, undoubtedly the status of the defense mechanism of the

bronchial tree plays a major role in determining which patients will be able to tolerate the aspirated material and which will develop lipid pneumonia. Guidry *et al.*[15] postulate that the relative infrequency of mineral oil granulomatosis despite the high incidence of mineral oil aspiration may be due to individual intolerance or sensitivity to oil in the lung.

Aspiration of oil is first dealt with by the primary defenses of the bronchial tree. These include the cough reflex, the cilia, and the mucous blanket lining the respiratory tract.[1,17] When these defenses are damaged or overwhelmed, mononuclear macrophages engulf the oil particles.[18,34] The more irritating animal oils (*i.e.*, mineral oil) also provoke a proliferation of septal and interstitial cells. Droplets and oil-laden macrophages permeate the septal and interstitial tissues, enter lymphatics, and may reach regional and hilar lymph nodes. A cellular and fibrous tissue reaction occurs along lymphatics. Oil remaining in alveoli provokes the formation of foreign body granulomas.

Since the interlobular septa are thickened by fibrosis and the septal lymphatics possibly plugged with oil and macrophages, it is understandable that these septa may be seen on roentgenograms.

The diagnosis of lipid pneumonia can seldom be made on the basis of chest roentgenograms alone. Two major types of roentgen pictures have been described, the diffuse and the nodular.[36,39] The former is characterized by fine linear spun glass densities described by Hampton *et al.*[16] and felt by some to be pathognomonic of lipid pneumonia.[15] In the nodular form soft tissue densities appear, varying from several centimeters in diameter to large lobulated masses. Lipid pneumonia in the nodular form is often difficult to differentiate from carcinoma of the lung and in many reports the diagnosis of lipid pneumonia was made first at thoractomy or after pneumonectomy for suspect carcinoma.[4,36,39] Since carcinoma may cause Kerley B lines when lymphangitic spread has occurred, the differentiation between these 2 entities may be further confused.

On the other hand the occurrence of Kerley B lines in lipid pneumonia may be a helpful diagnostic sign. This is especially true when the picture is that of the fairly characteristic bilateral lower lobe disease. The diagnosis may be further suspected if there has been little roentgen change over a period of time.[1,28] Sputum studies for fat droplets should be suggested when such a picture is recognized. In addition, a history of chronic mineral oil medication and lack of evidence for any of the other major causes of Kerley B lines should make one suspect lipid pneumonia even when the disease is not of the characteristic lower lobe distribution.

The prognosis of lipid pneumonia appears to be variable. If the intake and aspiration of the offending agent is not stopped, the course is that of progressive fibrosis and parenchymal destruction with loss of pulmonary function and eventual death from superimposed infection.[8] Cor pulmonale has recently been reported as a cause of death.[8]

If the disease is minimal and diagnosed early and the offending agent is discontinued, the lesions may clear on roentgenograms.[8] When the disease is more chronic or advanced, fibrosis is present and little clearing can be expected. The roentgenogram usually is stable over a long period of time but the lesions sometimes appear to decrease in size due to fibrosis, shrinkage of the lung and compensatory emphysema.[16] Several authors have reported progression of the disease even after ingestion of oil has been stopped.[15,38,39] Volk *et al.*[38] suggest that macrophages frequently disintegrate, setting free lipid droplets which may be reaspirated, thus producing a vicious cycle.

Although there are no long term follow-up studies of patients with lipid pneumonia, in general those with mild or moderate disease have a relatively good prognosis.

SUMMARY AND CONCLUSION

Thickening of interlobular septa may occur in lipid pneumonia and may be roentgenographically evident. Four cases are reported which illustrate this finding. Such septal thickening is not pathognomonic of lipid pneumonia; it also occurs in a limited number of other diseases. These are listed in the text. This finding, however, when viewed in the light of the clinical picture, may be a clue that lipid pneumonia is present and lead to the proper diagnosis as disclosed by other laboratory studies.

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PULMONARY SARCOIDOSIS*

ROENTGENOGRAPHIC OBSERVATIONS ON COURSE OF DISEASE

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SARCOIDOSIS is a common systemic granulomatous disease of unknown etiology which frequently and often spectacularly involves the thoracic lymph nodes and lungs. For this reason sarcoidosis is of special interest to radiologists. We have been impressed with the importance of the chest roentgenograms, not only in making the initial diagnosis, but also as an aid in predicting the ultimate prognosis of the patient. Our experience with a large group of patients with pulmonary sarcoidosis is presented below.

MATERIAL

We have reviewed the clinical records and available roentgenograms on all patients seen at the Columbia-Presbyterian Medical Center during the years 1932 to 1960 in whom the diagnosis of sarcoidosis was entertained. Positive histologic support was obtained in 250 cases consisting of the following: 54 cases without documented thoracic involvement; 51 cases with thoracic involvement but followed for less than one year (mainly asymptomatic patients); 10 cases with thoracic sarcoid involvement discovered at autopsy (in only 1 case was sarcoidosis responsible for death); and 135 cases with evidence of sarcoidosis on chest roentgenograms with clinical and roentgenographic follow-up of at least one year.

The present study is based upon this latter group of 135 patients. Of these 109 had an organ biopsy compatible with sarcoidosis (49 also had a positive Kveim test) and 26 had only a positive Kveim test biopsy[4,14] associated with a compatible clinical course. The age distribution at the onset of sarcoidosis was as follows:

	AGE GROUPS (YR.)							
	9–14	15–19	20–29	30–39	40–49	50–59	60–69	Total
Negro	2	7	38	29	20	7	1	104
White			11	11	4	3	2	31
Total	2	7	49	40	24	10	3	135

As can be seen, approximately three-fourths of our patients were of the Negro race. Onset of the disease in childhood is rare,[10,18] especially in Caucasians.

Serum globulin levels were above 3.0 gm. per cent in 68 per cent of the patients—in 80 per cent of the Negro patients compared to 32 per cent of the Caucasians. Of 112 patients having serum calcium determinations, 29 per cent had elevated values of 11 mg. per cent or higher. The clinically observed incidence of extrapulmonary involvement in the whole group was as follows: lymphadenopathy (extrathoracic) 56 per cent; liver 45 per cent; spleen 31 per cent; skin 28 per cent; eyes 23 per cent; muscle 14 per cent; salivary glands 10 per cent; bones of hands 8 per cent; cranial nerves 7 per cent; nasopharynx 5 per cent; heart 5 per cent; joints 5 per cent; lacrimal glands 4 per cent; and miscellaneous group 8 per cent including rib, marrow, larynx, vocal cord, kidney, stomach, thyroid and peripheral nerves.

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The historical, pathological and clinical aspects of sarcoidosis have been previously excellently reviewed and will not be elaborated upon here.[3,12,15,17,18]

In accordance with the findings on initial positive chest roentgenograms, our patients were placed in the following groups: (I) thoracic lymphadenopathy only; (II) thoracic lymphadenopathy and pulmonary densities; (III) pulmonary densities without lymphadenopathy; and (IV) predominant pulmonary fibrosis (Fig. 1). The distribution of white and Negro patients, as well as of the men and women, is quite similar in each of the above groups. This classification is used in presenting the roentgenographic findings and prognosis of patients with pulmonary sarcoidosis

ROENTGENOGRAPHIC FINDINGS IN PULMONARY SARCOIDOSIS

Since the roentgenographic manifestations of thoracic sarcoidosis may simulate a wide variety of diseases, accurate diagnosis obviously involves careful correlation of all the available clinical information. In the paragraphs to follow we will describe the salient features of sarcoidosis in the chest but cannot consider in detail all of the differential diagnostic possibilities.

THORACIC LYMPHADENOPATHY

Thoracic lymphadenopathy is the commonest and usually the earliest manifestation of sarcoidosis to be observed on chest roentgenograms. Bilateral hilar lymphadenopathy often with right paratracheal lymph node enlargement is characteristic of Boeck's sarcoid (Fig. 2, *A* and *B*). Of 76 patients observed initially with thoracic lymphadenopathy but without pulmonary parenchymal disease, 63 had bilateral hilar lymphadenopathy and 47 per cent of these also had recognizable right paratracheal lymphadenopathy. Although the lymphadenopathy is most readily detected and is often apparently more marked at the right hilus,[9,24] several of the cases had larger lymph nodes on the left. Often the lymph node enlargement is spectacular[3] having

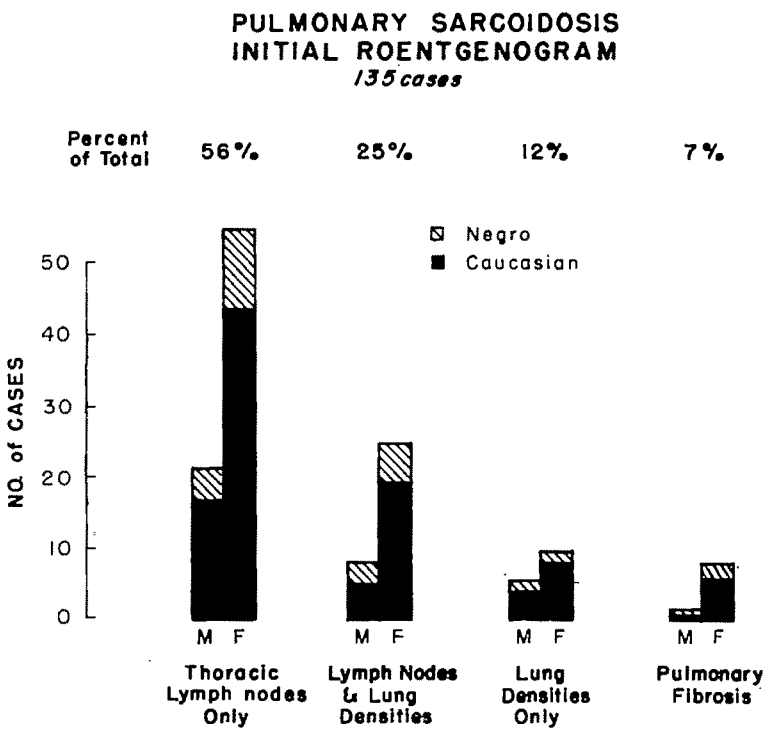


FIG. 1. Barograph showing grouping of the patients according to initial findings on chest roentgenograms.

earned the epithet "potato" lymph nodes in the earlier literature. Löfgren and Lundbäck[11] pointed out that bilateral hilar lymphadenopathy in adults is more characteristic of sarcoidosis than of tuberculosis.

Initially, in 13 of these 76 cases the hilar lymphadenopathy was unilateral; in 9 cases it was on the right and in 4 on the left. Eight of these patients also had right paratracheal lymph node enlargement. Six of the 13 cases were eventually observed to develop bilateral disease, whereas some or all of the others could have had such manifestations which were not documented by roentgen examination. Four of these 13 patients were positive reactors to tuberculin. Despite having well documented sarcoidosis, 2 of the 13 (of a total of 4, all Negro, in the entire series of 135 cases) eventually developed tuberculosis so that it is possible that the unilateral hilar lymphadenopathy in these 2 cases was stimulated by subclinical tuberculosis.

Recognizable enlargement of the left-sided mediastinal lymph nodes was present in less than 10 per cent of the cases. Anterior mediastinal lymphadenopathy was even less common.

Wigh and Montague,[23] reporting from this institution, pointed out that anterior mediastinal lymphadenopathy is much more characteristic of lymphomas than of sarcoidosis. They also noted a characteristic "squaring" of the right lower hilus due to enlargement of an intrapulmonary lymph node contrasted against air in the right lower lobe bronchus. Despite the huge size of the hilar lymph nodes in many cases, atelectasis is not a very common sequel in sarcoidosis perhaps because of the characteristic absence of matting and fixation of the involved lymph nodes. Only 2 of our cases had lobar collapse (1 middle lobe and 1 left lower lobe). Caval obstruction by these lymph nodes is virtually unknown.

While thoracic lymphadenopathy is commonly present at the onset of clinical sarcoidosis, we have encountered several patients in whom it did not appear until years after involvement of the skin, salivary glands, eyes or liver.

Thoracic lymph node enlargement may

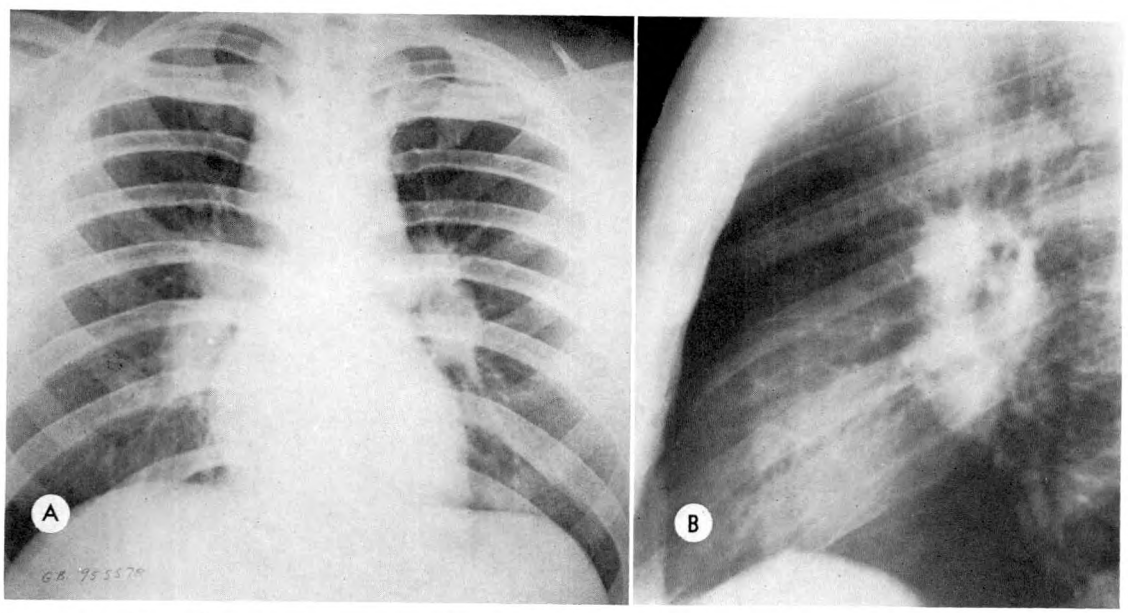


FIG. 2. (*A*) Frontal chest roentgenogram demonstrating a typical appearance of enlarged hilar and right paratracheal lymph nodes in sarcoidosis, which cleared completely without a phase of lung parenchymal involvement. (*B*) In lateral projection the hilar lymph node enlargement is well demonstrated. Note the typical absence of anterior mediastinal involvement.

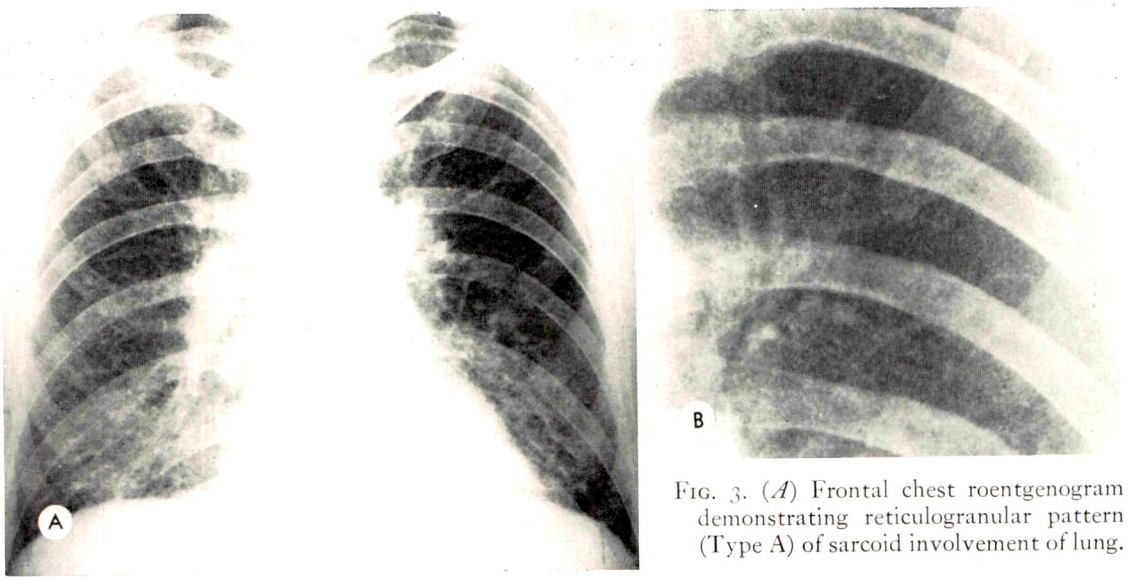


Fig. 3. (*A*) Frontal chest roentgenogram demonstrating reticulogranular pattern (Type A) of sarcoid involvement of lung. (*B*) Magnified view of lung field to better show the fine reticular pulmonary infiltration.

be responsible for chest or shoulder pain in a few cases,[8] but, as might be expected, it is not usually associated with respiratory tract symptoms (cough, dyspnea or hemoptysis). Indeed, the presence of such symptoms, even though the roentgenograms fail to show pulmonary disease, usually implies bronchial or pulmonary sarcoidosis. Although only 17 of our 76 patients presenting with thoracic lymphadenopathy had such respiratory symptoms, more than 71 per cent of these subsequently developed roentgenographic pulmonary densities. On the other hand, among the 59 patients without respiratory symptoms only 17 per cent eventually developed pulmonary densities. If endobronchial biopsies are obtained at this stage, sarcoidosis of the bronchial mucosa and/or lung can sometimes be demonstrated histologically[5,11]

PULMONARY PARENCHYMAL DENSITIES

Pulmonary parenchymal densities in sarcoidosis are typically bilateral and extensive but with wide variations from case to case. The most commonly spared regions are the extreme lung apices and extreme bases, although rarely either of these areas may be predominantly involved. Unilateral lung involvement appears to be extremely unusual—in only 1 of our 81 cases with pulmonary involvement was the disease almost completely confined to one lung.

The character of the pulmonary densities ranges widely from a fine reticular accentuation of pulmonary interstitial markings to large confluent areas not unlike those seen in bronchopneumonia or metastatic tumor (Fig. 3–6, inclusive). Perihilar linear densities are often seen at the onset of pulmonary involvement.[20] In our entire series of 135 cases, 81 had roentgenographic evidence of pulmonary parenchymal involvement. This involvement was observed to follow thoracic lymphadenopathy in 22 cases, to be present at the time of the initial diagnosis accompanied by thoracic lymphadenopathy in 33 cases, and to be present at the time of the initial clinical diagnosis not associated with thoracic lymphadenopathy in 16 cases. In 10 additional cases impressive pulmonary fibrosis was already present on initial roentgenographic examination.

For purposes of analysis we have classified the roentgenographic manifestations of active pulmonary sarcoidosis into 4 types (reserving the stage of predominant pulmo-

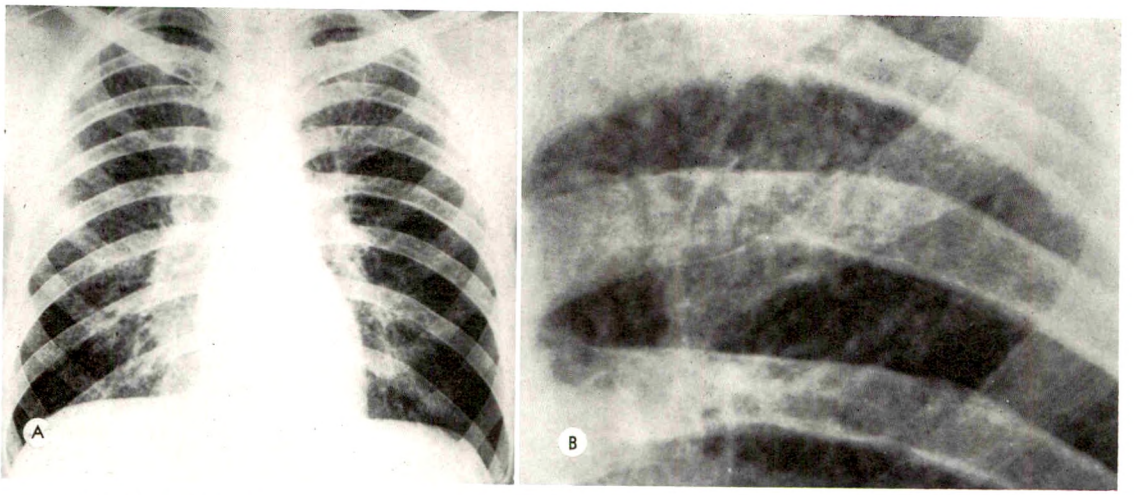


FIG. 4. (*A*) Frontal chest roentgenogram demonstrating miliary pattern (Type B) of sarcoid involvement of lung. (*B*) Magnified view of lung field to better show the miliary densities.

nary fibrosis for another category):

Type A. Reticulogranular (in extreme a "ground-glass" appearance)—13 patients (7 Negro)
Type B. Miliary (1–3 mm. diameter densities)—20 patients (18 Negro)
Type C. Nodular (4–9 mm. diameter densities)—21 patients (15 Negro)
Type D. Large nodular or confluent densities (10 or more mm. in diameter)—17 patients (13 Negro)

The patients were classified according to the largest predominant type of pulmonary densities seen on serial roentgenograms, although some 30 per cent were observed at other times to have predominant pulmonary densities of a smaller type.

Typically in sarcoidosis, as the pulmonary infiltrations progress, reciprocal regression of thoracic lymphadenopathy occurs (Fig. 8, *A*, *B* and *C*). Minor degrees of lymphadenopathy, however, may be obscured by the lung densities. Regression of the lymphadenopathy despite progressive lung involvement would not be expected in the case of metastatic neoplasm or lymphoma, and this feature therefore may be helpful in the differential diagnosis.[5] Although uncommon, thoracic lymphadenopathy may persist after clearing of the lung densities as happened in 2 of our cases.

Inexplicably, the lymph node and parenchymal densities in sarcoidosis may regress spontaneously at any stage of the disease (Fig. 8, *A*, *B* and *C*; and 9, *A* and *B*). Once the roentgenographic findings return to normal, recurrences in the chest are rare. In this series in only 5 cases did the thoracic disease recur after apparent complete clearing—in 4 cases on interruption of steroid therapy and in the other following a normal pregnancy. An additional case showed almost complete spontaneous remission of the lung disease followed by exacerbation and eventual pulmonary fibrosis.

While it is clear that steroid therapy may relieve clinical symptoms and cause regression of the thoracic sarcoidosis, we, like others,[16,22] are not yet certain of its effect on the ultimate course of this disease. The 45 patients in our series treated with steroid fared worse ultimately than those not so treated. The same situation was noted in other series[7,16] and is evidently related to the selection of the more unfavorable cases for steroid therapy. Only a single case of active tuberculosis occurred in the steroid treated group (1 of the 40 in this group who were initially tuberculin negative).

Pleural effusion is very rare and should suggest complicating tuberculosis, other pulmonary disease, or cardiac failure (or

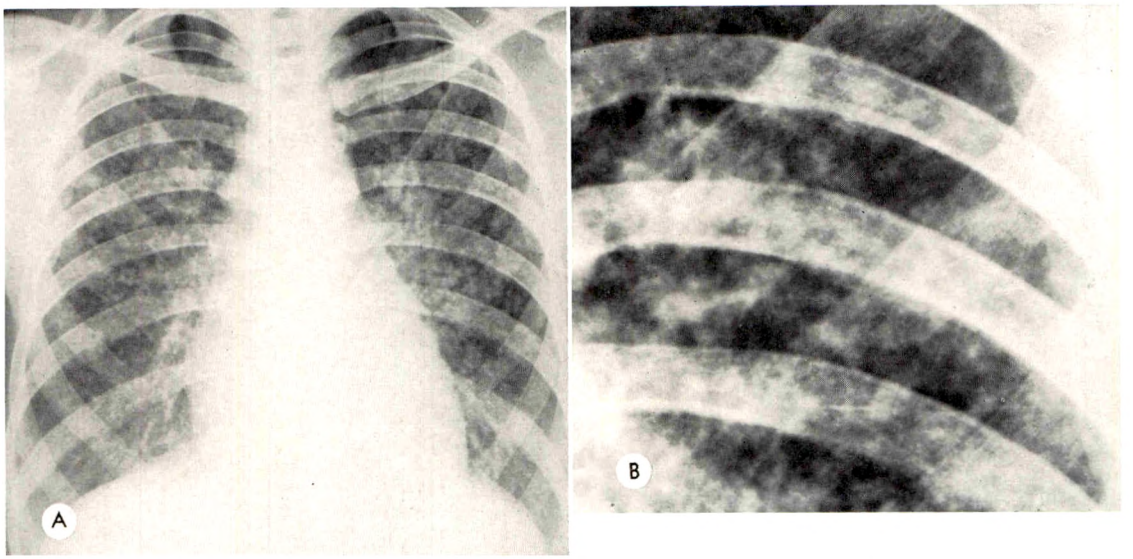


FIG. 5. (*A*) Frontal chest roentgenogram demonstrating nodular pattern (Type C) of pulmonary densities in sarcoidosis. (*B*) Magnified view of lung field showing the nodular densities.

that the primary diagnosis is incorrect). One of our patients did have a small right pleural effusion associated with active pulmonary sarcoidosis. In 3 other cases, however, pleural effusions heralded the onset of complicating tuberculosis.

Hilar or parenchymal calcifications which are not infrequently seen in the presence of thoracic sarcoidosis are almost always the consequence of prior tuberculous or fungous infection.[11] Such calcifications were present in 26 per cent of our series. Lymph node calcification was observed to develop in only 2 cases, in 1 being attributable to calciferol administration; renal and other soft tissue calcifications became manifest simultaneously. The other patient had chronic pulmonary sarcoidosis with hyper-

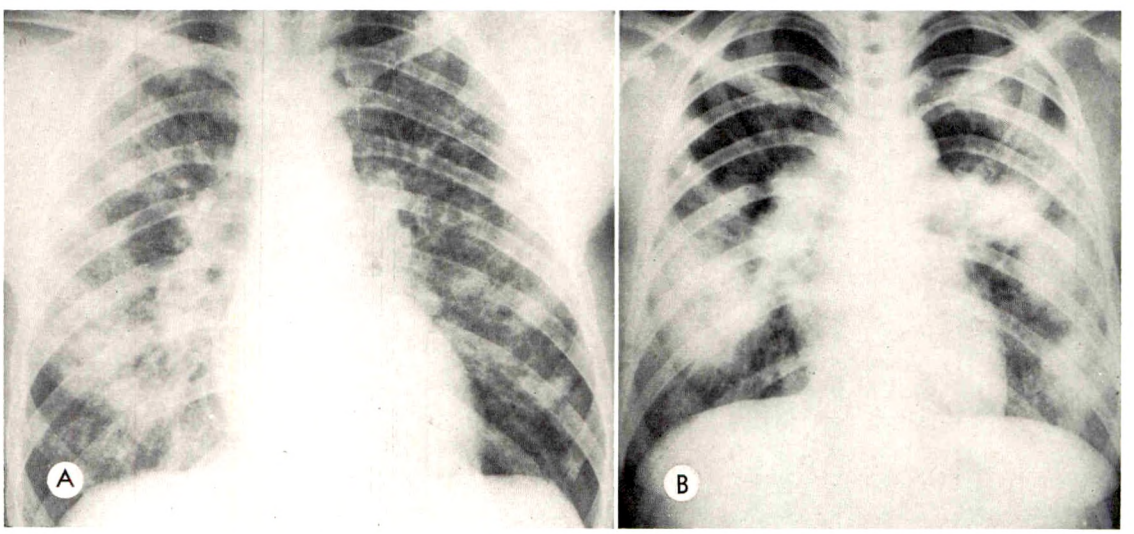


FIG. 6. (*A* and *B*) Frontal chest roentgenograms demonstrating large nodular or confluent pulmonary densities (Type D-1 cm. or more in diameter) in sarcoidosis. Note in *B* the huge size that these tumor-like densities may attain.

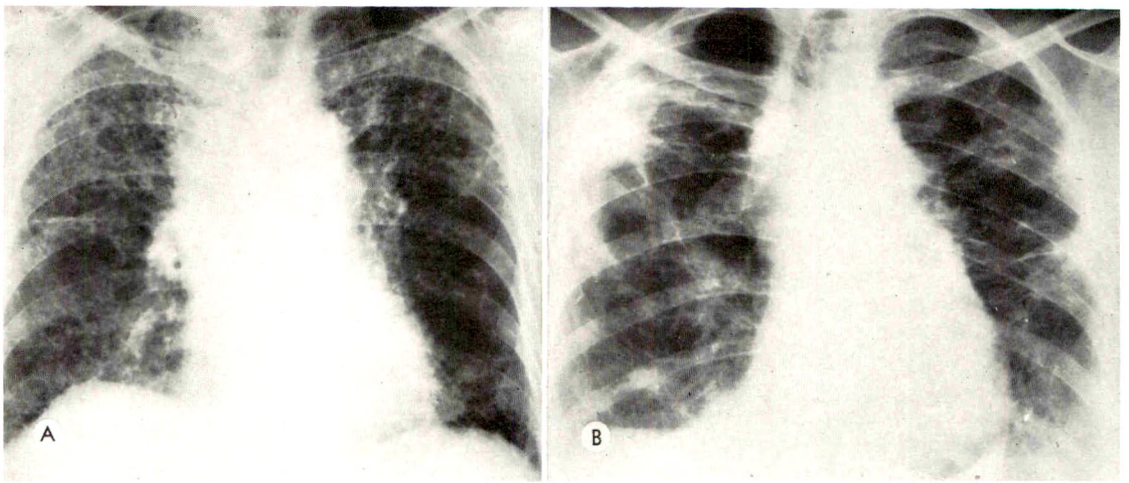


FIG. 7. (*A*) Frontal chest roentgenogram demonstrating severe pulmonary fibrosis in sarcoidosis. The multiple small radiolucencies represent focal emphysema or in some regions bronchiectasis. Gross fibrosis was already present when this patient first sought medical attention. (*B*) Pulmonary fibrosis in sarcoidosis with larger areas of emphysema and upward retraction of the hilar shadows.

calcemia (up to 15.3 mg. per cent). Eventually extensive calcification of hilar and mediastinal lymph nodes occurred, a very rare manifestation of sarcoidosis.[5] In the other cases thoracic calcification remained unaltered throughout the course of observation and was of no help in the differential diagnosis.

Despite the spectacular pulmonary densities seen in active sarcoidosis, the patients often have disproportionately mild pulmonary symptoms, and death from the lung infiltrations alone in the absence of fibrosis virtually never occurs. No deaths occurred in our series from the pulmonary disease alone before extensive fibrosis had developed—possibly steroid therapy may have averted this in some. In a certain portion of cases, severe progressive pulmonary fibrosis is a consequence of lung sarcoidosis (Fig. 7, *A* and *B*; and 10, *A* and *B*). This development is gradual, usually requiring several years, and is not commonly accompanied by lymphadenopathy.

PULMONARY FIBROSIS

Late severe pulmonary fibrosis with secondary lung distortion and destruction is the most serious consequence of pulmonary sarcoidosis and directly or indirectly is responsible for most of the deaths. Nineteen of our 71 cases with active sarcoidosis in the lungs were observed to develop moderate to severe pulmonary fibrosis. Twelve other cases developed minimal residual focal fibrosis of no apparent consequence. An additional 10 cases were first observed after pulmonary fibrosis was well established, in some cases in the presence of cor pulmonale. The latter patients had presumably gone through the earlier stages of pulmonary sarcoidosis with insufficient symptoms to cause them to seek medical attention.

As stated by Felson,[2] the major roentgenographic criteria for pulmonary fibrosis (while not always reliable) include narrow linear, strand-like pulmonary densities, which persist for long periods of time and which are associated with evidence of lung shrinkage as manifested by retraction and distortion of fissures, hili, vessels, bronchi and mediastinal or other pleural surfaces. By means of these signs the conglomerate densities produced by lung contraction in the fibrotic stage (Fig. 7, *A* and *B*) can usually be distinguished from the confluent pulmonary densities (Type D) of the granulomatous phase of pulmonary sarcoidosis (Fig. 6, *A* and *B*). When symptoms of

severe respiratory failure or cor pulmonale were present, the pulmonary fibrosis was conspicuous.

Dilatation of the central pulmonary arteries secondary to pulmonary arterial hypertension as well as right heart enlargement is often seen at this stage of the disease.

A multicystic pattern in the lungs is a frequent finding in the late fibrotic stage of sarcoidosis, the lucent regions representing secondary emphysema or sometimes bronchiectasis.[2,6,12,18] Often conspicuous upward retraction of the hilar structures occurs and the cystic changes are usually more marked in the mid and upper lung fields (Fig. 7, *A* and *B;* and 10, *A* and *B*). At this stage the roentgenographic appearance is nonspecific and may be identical with that resulting from the destructive and fibrotic consequences of tuberculosis, fungus infections, chronic bronchiectasis, Hamman-Rich syndrome, scleroderma, beryllosis, or other types of pneumoconiosis. In our opinion a substantial number of the cases which we see with idiopathic pulmo-

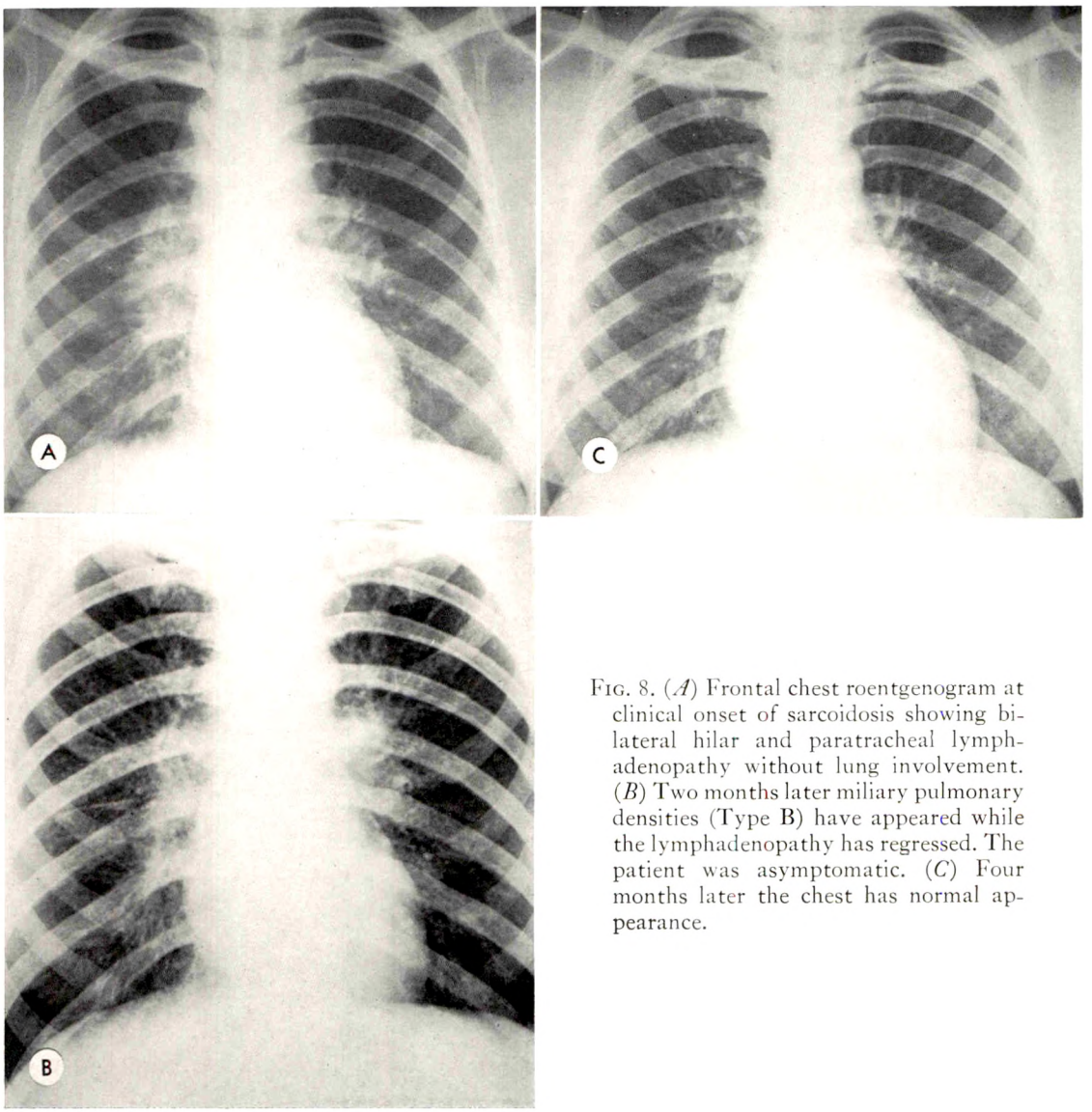


Fig. 8. (*A*) Frontal chest roentgenogram at clinical onset of sarcoidosis showing bilateral hilar and paratracheal lymphadenopathy without lung involvement. (*B*) Two months later miliary pulmonary densities (Type B) have appeared while the lymphadenopathy has regressed. The patient was asymptomatic. (*C*) Four months later the chest has normal appearance.

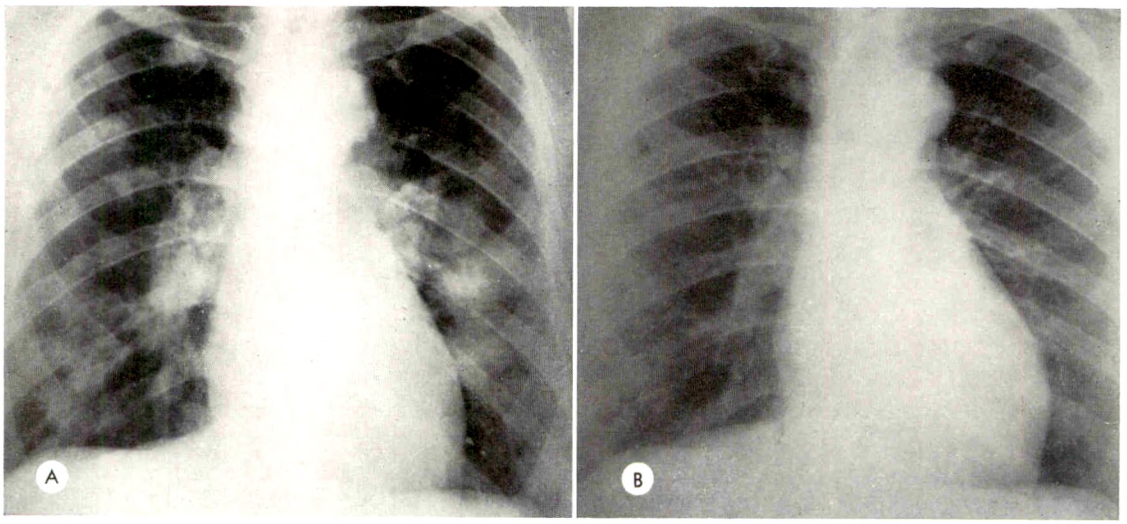


FIG. 9. (*A*) Frontal chest roentgenogram demonstrating involvement of hilar lymph nodes and large nodular densities in lungs at clinical onset of sarcoidosis with respiratory symptoms. (*B*) One year later the patient was asymptomatic and the chest roentgenogram was normal.

nary fibrosis represent the late consequences of sarcoidosis after disappearance of the characteristic granulomatous lesion.

PROGNOSIS IN RELATION TO INITIAL ROENTGENOGRAPHIC FINDINGS

James[16] has pointed out that sarcoidosis would remain a relatively benign disease but for the development of certain devastating complications, which are due to irreversible fibrosis of the lungs, eyes, or other organs and to the effects of an abnormal calcium metabolism on the kidneys. Most fatalities caused by sarcoidosis result from respiratory insufficiency and cor pulmonale. For this reason we have utilized the development of moderate to severe pulmonary fibrosis as a criterion of major prognostic importance.

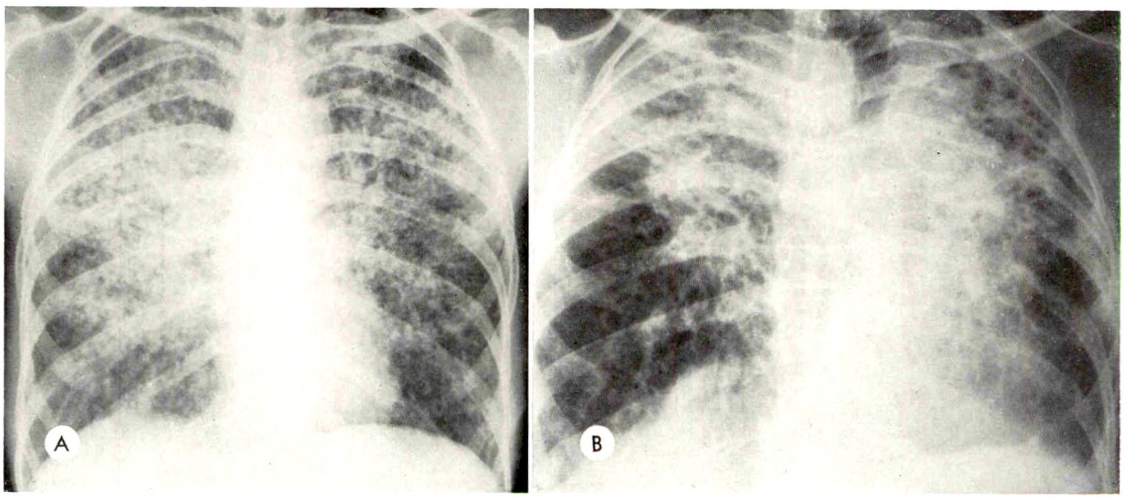


FIG. 10. (*A*) Frontal chest roentgenogram demonstrating confluent miliary and nodular pulmonary densities (Types B and C) in sarcoidosis. (B) Six years later severe pulmonary fibrosis with particularly marked contraction of the left upper lobe has appeared.

Table I

SUMMARY OF THE FOLLOW-UP INFORMATION ON 76 PATIENTS WITH ONLY THORACIC LYMPHADENOPATHY ON INITIAL EXAMINATION (AVERAGE ROENTGEN FOLLOW-UP 8 YEARS)

Improved				
Without known phase of lung disease		41		
Complete	33			
Partial	8			
After development of pulmonary densities		14		
Complete	8			
Partial	6			
Total			55	(72%)
Unchanged				
Without lung disease		13		
After development of lung densities		2		
Total			15	(20%)
Worse				
Developed moderate to severe pulmonary fibrosis			6	(8%)
			76	(100%)

I. INTRATHORACIC LYMPHADENOPATHY WITHOUT PULMONARY DISEASE

(Fig. 2, *A* and *B;* and 8, *A*, *B* and *C*)

In Table I a summary of the follow-up information is given of 76 patients who presented with only thoracic lymphadenopathy on initial examination. In 72 per cent of these patients the lymphadenopathy cleared completely or nearly completely, one-fourth of the cases having experienced a phase of pulmonary involvement, usually appearing within 1 year of clinical onset, but ranging between 1 month and 7 years. None of these patients had respiratory symptoms when last seen, and only 5 had persistent evidence of extrathoracic sarcoidosis. Twenty-two of the 41 patients showing complete clearing did so in less than 1 year and only 2 after 4 years of observation.

A relatively large group, 20 per cent, remained substantially unchanged roentgenographically (2 after having developed lung disease) after an average period of observation of more than 7 years. All of these patients were Negro and 12 of 15 were women. None of these patients had pulmonary symptoms at the end of the observation period, but 2 had died (1 by suicide and 1 of sarcoidal cirrhosis of the liver), 1 had developed and recovered from pulmonary tuberculosis, and 3 were symptomatic with extrathoracic sarcoidosis.

In 8 per cent of the whole group (6 cases), pulmonary fibrosis of moderate to severe degree had developed after varying periods of time ranging from 2 to 20 years. Four of these 6 patients developed the initial lung densities from 2 to 7 years following thoracic lymphadenopathy. One of these patients died of chronic lung disease complicated by pyelonephritis and the other 5 have persistent pulmonary symptoms (cough and dyspnea).

II. THORACIC LYMPHADENOPATHY AND PULMONARY DENSITIES

(Fig. 6, *A* and *B;* and 9, *A* and *B*)

In Table II the roentgenographic results are given of 33 patients who presented with thoracic lymphadenopathy and pulmonary densities on initial examination. Note that 76 per cent of these patients had normal or markedly improved chest roentgenograms at the end of the observation period, which averaged 5 years. Two patients, however, had congestive heart failure with exertional dyspnea, possibly but not necessarily due to myocardial sarcoidosis. Only 1 patient had clinical evidence of active extrathoracic sarcoidosis. Of the 19 patients whose roent-

Table II

OUTCOME BY ROENTGENOGRAPHIC EXAMINATION OF 33 PATIENTS WITH THORACIC LYMPHADENOPATHY AND PULMONARY DENSITIES ON INITIAL EXAMINATION

Improved		25	(76%)
Complete	19		
Partial	6		
Unchanged		1	(3%)
Worse			
Developed moderate to severe pulmonary fibrosis		7	(21%)
		33	(100%)

genograms became normal, 9 showed no evidence of disease in less than 1 year and only 1 after 4 years of observation.

The 1 patient showing no change on the chest roentgenogram had no pulmonary symptoms but died after 3 years' observation of a bleeding peptic ulcer, perhaps related to steroid therapy.

In 21 per cent (7 cases) of this group, evidence of moderate to severe pulmonary fibrosis developed after periods of observation ranging between 1 and 15 years. One of these patients died of cor pulmonale with respiratory failure, while 2 have persistent severe dyspnea, 1 of these with episodes of hemoptysis. The remaining 4 patients are virtually asymptomatic, although 2 are continued on steroid therapy.

III. PULMONARY DENSITIES WITHOUT THORACIC LYMPHADENOPATHY

(Fig. 4, *A* and *B;* and 9, *A* and *B*)

In Table III a summary of the follow-up information is given of 16 patients who presented with pulmonary densities but without thoracic lymphadenopathy on initial examination. Ten (63 per cent) of this group showed complete clearing of the densities or significant improvement after an average period of observation of more than 8 years. None of these patients had persistent clinical symptoms secondary to sarcoidosis although 1 patient has been continued on chronic steroid therapy. Of the 6 patients who cleared completely, 1 did so in less than 1 year and another after more than 4 years.

TABLE III

SUMMARY OF THE FOLLOW-UP INFORMATION ON 16 PATIENTS WITH PULMONARY DENSITIES WITHOUT THORACIC LYMPHADENOPATHY

Improved		10	(63%)
Complete	6		
Incomplete	4		
Worse		6	(37%)
		16	(100%)

Six (37 per cent) of this group developed moderate to severe pulmonary fibrosis while under observation. One of these patients died after 9 years with cor pulmonale while 2 others had symptoms of cough, dyspnea, and hemoptysis after 7 and 10 years of observation, respectively. The remaining 3 patients were only mildly symptomatic.

IV. PULMONARY FIBROSIS AT TIME OF INITIAL MEDICAL OBSERVATION

Ten of our 135 patients with well documented pulmonary sarcoidosis already had moderate to severe pulmonary fibrosis on initial roentgen examination (Fig. 7, *A* and *B*). Four of these were thought to have some roentgenographically persistent sarcoidal infiltrations in the lungs when first seen, one also showing hilar lymph node enlargement. While under observation, 3 of these patients died of cor pulmonale and respiratory insufficiency and another died primarily of myocardial disease. Five others had persistent dyspnea and cough, while the remaining patient was essentially asymptomatic despite severe roentgen changes consistent with pulmonary fibrosis. Only 1 of the patients had evidence of active extrapulmonary sarcoidosis—the appearance of skin plaques at the end of the observation period. None of these patients showed improvement on chest roentgenograms.

The incidence of sarcoidosis in the Negro population of the United States is considerably greater than in the Caucasian population.[1,16] Some believe that thoracic sarcoidosis, once diagnosed, is more severe in the American Negro.[22] Among 71 patients with active sarcoidal pulmonary densities, significant pulmonary fibrosis was observed to develop in 8 of 38 Negro females, 6 of 16 Negro males, 4 of 9 white females, and 1 of 8 white males.

A total of 8 patients, all female—7 Negro, died as a direct consequence of sarcoidosis: 6 with irreversible pulmonary fibrosis and cardiorespiratory failure (3 of these having presented initially with severe

pulmonary fibrosis); and 1 each in whom death was secondary to cardiac or hepatic involvement. Two patients died of causes possibly related to steroid therapy, suicide in 1 case and bleeding peptic ulcer in another. Three other patients died of unrelated causes.

DISCUSSION OF THE COURSE OF PULMONARY SARCOIDOSIS

At the International Conference on Sarcoidosis in 1960,[16] investigators agreed that sarcoidosis in various countries was basically the same disease despite some local variations in epidemiology and in the incidence of certain manifestations.

Unfortunately, precise comparison of the prognosis of thoracic sarcoidosis in our series with that of other large series reported in the literature is virtually impossible because of stated and unstated differences in classifying the patient material, the roentgenologic and clinical follow-up, and the ultimate outcome of the disease in the chest. Nevertheless, when compared on the basis of the thoracic disease present on initial roentgen examination, with due consideration for the better prognosis of cases with erythema nodosum,[7,9] the final outcome of the chest disease appears to be very similar in the recently reported large series.[1,7,9,19–22]

Löfgren's[9] careful work showed a benign course of the "bilateral hilar lymphoma syndrome" due to sarcoidosis when patients presented initially with erythema nodosum. No one has disputed this conclusion although erythema nodosum appears in this connection to be considerably more common in Sweden than elsewhere. All 11 of our patients (9 Negro females) who had erythema nodosum at clinical onset of sarcoidosis were followed until they were clinically and roentgenologically normal, except for the one suicide.

In the majority of cases of thoracic sarcoidosis, initially thoracic lymph node enlargement is noted on roentgenograms. Some believe that this is virtually always true.[8,24] Since the thoracic lymphadenopathy *per se* uncommonly produces symptoms, this phase of the chest disease is detected most often either on routine survey examinations or when extrathoracic manifestations of sarcoidosis cause the patient to seek medical attention. The presumption is that a substantial number of individuals may have subclinical sarcoidosis with thoracic lymphadenopathy, with or without progression to pulmonary densities, which is never discovered if spontaneous recovery occurs. Most of the medically observed patients are those with symptom producing involvement of the respiratory tract or other systems.

Also supporting the idea that earlier phases of thoracic sarcoidosis may not be detected is the fact that a number of individuals seek medical attention only after significant pulmonary fibrosis is present, presumably having progressed asymptomatically through phases of thoracic lymph node and pulmonary granulomatous disease. In Table IV are given the results in our 135 cases when reasons for initial chest roentgen examination were related to the type of pulmonary involvement found. Note that when the initial examination was made primarily because of respiratory symptoms, the great majority of patients had detectable lung involvement and about 14 per cent already had moderate to severe pulmonary fibrosis.

In our experience 71 per cent of the patients presenting with only thoracic lymphadenopathy never developed pulmonary densities; in three-fourths the densities cleared completely or nearly so and in the rest they remained unchanged for a number of years. This tendency for the thoracic lymph nodes to persist unchanged for prolonged periods was particularly common in Negroes. About 29 per cent of the patients were observed to develop pulmonary densities, which in most cases cleared completely or improved. Of the entire group presenting with only thoracic lymphadenopathy, about 8 per cent have been observed roentgenographically to develop moderate to severe pulmonary fibrosis.

TABLE IV

INITIAL ROENTGENOGRAPHIC FINDINGS

Reason for Examination	Thoracic Lymphadenopathy (no. of cases)	Thoracic Lymphadenopathy and Pulmonary Densities (no. of cases)	Densities Only (no. of cases)	Predominant Pulmonary Fibrosis (no. of cases)
Routine Survey	12	3	1	0
Erythema Nodosum	8	2	1	0
Nonrespiratory Symptoms	39	5	3	2
Respiratory Symptoms	17	23	11	8
	76	33	16	10

Once visible pulmonary densities occur in sarcoidosis, the ultimate prognosis of the patient becomes considerably more grave. Of our 71 patients with pulmonary densities, whether present initially or developing after a phase of thoracic lymphadenopathy, 19 (27 per cent) were observed to develop moderate to severe pulmonary fibrosis. This appeared more likely in patients who developed pulmonary densities after prolonged periods of observed lymphadenopathy or chronic sarcoidosis of other systems and in those patients having lung densities without obvious lymphadenopathy when first examined. The latter presumably represented patients who had already experienced regression of the lymphadenopathy phase of the disease. Of 33 patients presenting with lung densities and thoracic lymphadenopathy, 21 per cent developed moderate to severe pulmonary fibrosis, while this consequence was observed in 37 per cent of patients presenting with lung densities without definite lymphadenopathy.

In our experience moderate to severe pulmonary fibrosis developed more commonly in those patients with the larger pulmonary parenchymal densities, the incidence of this consequence being: 1 of 13 patients with reticulogranular pulmonary densities (Type A); 4 of 20 with miliary densities (Type B); 8 of 21 with nodular densities (Type C); and 6 of 17 with large nodular pulmonary densities (Type D).

The recurrence of thoracic sarcoidosis after roentgenograms show spontaneous complete clearing is very rare and often related to pregnancy—especially in the postpartum period.[16,19,22]

SUMMARY

1. One hundred thirty-five cases of pulmonary sarcoidosis were analyzed with respect to roentgenographic findings and prognosis. The following patterns were observed on the initial chest roentgenograms in decreasing order of frequency and increasing order of prognostic gravity: (I) thoracic lymphadenopathy alone (with or without later development of pulmonary densities); (II) thoracic lymphadenopathy associated with parenchymal densities ranging in appearance from reticulogranular to large and conglomerate; (III) parenchymal densities alone; and (IV) pulmonary fibrosis.

2. The outcome is almost uniformly good when thoracic lymphadenopathy clears without the appearance of pulmonary densities or when it is associated with erythema nodosum at the onset of disease.

3. Thoracic lymphadenopathy may persist unchanged over a period of many years.

4. The most serious consequence of pulmonary sarcoidosis is irreversible lung damage with fibrosis.

5. Characteristic features of thoracic lymphadenopathy in sarcoidosis are bilateral hilar lymphadenopathy with or

without right paratracheal lymphadenopathy, regression during development of parenchymal densities, and lack of anterior mediastinal lymphadenopathy.

6. When spontaneous remission occurs and chest roentgenograms are normal, recurrences are extremely rare, in contrast to steroid-induced remissions which may be transient.

7. Pleural effusions are quite rare in thoracic sarcoidosis and when present should suggest another disease such as tuberculosis, neoplasm or cardiac failure.

8. When the outcome of our cases, in terms of late irreversible pulmonary fibrosis, was compared with other large series in the literature, the results were similar.

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TRACHEOBRONCHIOMEGALY*

THE MOUNIER-KUHN SYNDROME

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TRACHEOBRONCHIOMEGALY is a distinctive clinico-roentgenologic condition consisting of marked dilatation of the trachea and major bronchi associated with chronic respiratory tract infection. The syndrome is rare, often begins in childhood and is thought to be due to a congenital defect of the elastic and muscle fibers of the tracheobronchial tree. The simple chest roentgenogram may furnish the initial clue to the diagnosis. In this paper the clinical and roentgen findings in 4 patients with this disease pattern are described. A fifth case presented dilatation of the bronchi but not of the major portion of the trachea. This entity has been reported previously under a variety of names including tracheobronchiopathia malacia,[14] idiopathic megatrachea with tracheomalacia,[3] trachiectasis,[7] tracheomegaly,[17] and tracheobronchiectasis.[8] We prefer our designation, tracheobronchiomegaly, since it is simple, anatomically descriptive and avoids confusion with phonetically allied conditions such as tracheal malacia and tracheal ectasia (aerial goiter).[19]

HISTORICAL ASPECTS

The first comprehensive description of the pathologic changes in tracheobronchiomegaly is credited to Czyhlarz[2] who in 1897 noted marked atrophy of the longitudinal elastic fibers and thinning of the muscularis in a postmortem specimen. Asserting that "one cannot avoid the rather vague idea of a congenital weakness of the walls" he employed the term "pulsion diverticulum" in the title of his report. An earlier report of the same lesion was made by Rokitansky.[1,12] It was not until 1929 that the second anatomic description of this disease was recorded by another pathologist, Kaufman,[9] who wrote that "in chronic catarrhs, circumscribed, deep bulgings are occasionally seen (ectasias) or diffuse, spindle-shaped dilatations, both usually in the membranous part (posterior wall) often with numerous saccular diverticula between the cartilaginous rings."

Mounier-Kuhn,[11] in 1932, published the first clinical description of the condition which is designated occasionally as the "Mounier-Kuhn syndrome." He referred to his case as one of "dilatation of the trachea." His illustration also showed dilated bronchi and saccular bronchiectasis of the left lung. Since Mounier-Kuhn's original report, approximately 10 additional cases have been recorded in the literature.

PATHOGENESIS

An understanding of the pathogenesis of tracheobronchiomegaly must be based upon an awareness of the variety of out-pouchings of the tracheobronchial tree which have been disclosed by roentgen and postmortem studies. Nielsen,[12] using the broad designation of "diverticulum" to include any type of out-pouching, has classified these structures according to mode of origin. She has separated them into 3 categories, as follows:

1. Rudimentary, or supernumerary, bronchi are short and cylindrical. They always arise from the right aspect of the trachea near the carina and contain all structural elements of the tracheal wall.

2. Diverticula of acquired origin have a narrow neck and may range in size from a few millimeters to 3 or more centimeters. They usually contain viscid mucus and are thought to originate as cystic dilatations of

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the ducts of paratracheal mucus glands. These develop in response to chronic irritation and may be distended further by increased intratracheal or intrabronchial pressure produced by coughing. They arise at the junction of the cartilaginous and membranous tissues. Bronchographic examination may reveal them as bud-like sacs, 1 or 2 mm. in diameter, projecting from the bronchi. Such "diverticula" are considered pathognomonic of chronic bronchitis but when they assume unusually large proportions may be mistakenly regarded as true diverticula. Moderate dilatation and atrophy of the trachea is often an associated finding.

3. The third type of tracheobronchial out-pouching is a broad diverticulum-like protrusion of redundant nonmuscular segments of membrane between transverse bands of muscle fibers of the trachealis muscle which connect the posterior tips of the "U" shaped tracheal cartilages. These out-pouchings are generally found throughout the entire length of the trachea and major bronchi and there is associated marked increase in size of the trachea and major bronchi. It is into this category that patients with tracheobronchiomegaly fall. Pathologically, this group is characterized by atrophic changes in elastic and muscle fibers. Nielsen[12] designates some cases of tracheobronchiomegaly as "diffuse tracheobronchiectasies without diverticulum formation," stating that the same pathologic process is at fault and that allowance must be made for transitional forms. Her own case which she classifies under this group is reported as a case of multiple tracheal diverticula.

Other case reports in which the term "diverticulum" appears in the title encompass the entire gamut of tracheobronchial out-pouchings and hence the term has little specificity or meaning.[5,6,10,15] Because of this confusion in terminology and lack of histologic study in most cases reported, it is difficult to classify all cases.

There remains a type of out-pouching characterized by a single, large, air-containing sac possessing a wide mouth and communicating with the lumen of the trachea. This is the so-called aerial goiter, also termed tracheocele, aerocele, tracheal hernia, tracheal ectasia and less accurately, tracheal diverticulum. Although these are usually ascribed to a localized inherent weakness of the posterior tracheal wall, the effects of occupation and infection are also considered to influence their development. Thus, individuals whose work requires unusually high levels of intratracheal pressure are known to develop this type of lesion. Classic examples are the aerial goiters found in drill sergeants, the Egyptian minaret crier and musicians who play wind instruments. Severe or prolonged coughing, for the same reason, is also cited as a cause of this lesion. Such an instance was reported in a 3½ year old boy who developed a swelling in the neck immediately after a prolonged spell of violent coughing. Aspiration revealed this to be an aerocele.[16]

Lesser degrees of uniform dilatation of the trachea are seen in other conditions. Shanks and Kerley[20] noted that widening of the trachea occurs characteristically in the presence of pulmonary fibrosis. Mounier-Kuhn[11] felt that slight dilatation of the trachea and major bronchi was not unusual in patients with chronic cough, bronchiectasis or in individuals whose occupation involved excessive vocal or pulmonary effort. However, the degree of dilatation observed in tracheobronchiomegaly is much more marked than in these instances.

Tracheobronchiomegaly has been ascribed to a congenital defect of elastic and muscle fibers of the tracheobronchial tree by most authors. Claims for the congenital etiology of this lesion are based upon histologic study revealing underdeveloped elastic and muscle tissue and upon the early age of onset in some cases. Mounier-Kuhn's original patient, aged 42, manifested severe respiratory symptoms in infancy and by the age of 7 had a chronic cough of whooping character which persisted throughout his adult life. Doyle and co-workers'[4] pa-

tient, aged 8 years, had also suffered from cough with frequent respiratory infections from infancy. The remainder of the patients gave histories of many years of respiratory difficulty although they were first seen as young adults.

Postmortem specimens from 4 cases,[1,2,7,14] and several biopsy specimens from another case[17] lend supporting evidence to the theory of the congenital basis of this lesion. Czyhlarz[2] noted thinning of the muscularis and marked atrophy of the longitudinal elastic fibers. Brenner and Krauter[1] also noted a decrease in the number of the elastic fibers without evidence of inflammation in the tracheal wall at postmortem examination. In their report the trachea is described as "striking," measuring 9 cm. in circumference and showing equal and proportionate enlargement of both the cartilaginous and membranous portions, a point which they regard as favoring a congenital enlargement, since acquired (mechanical) dilatation would involve primarily the distensible, membranous wall which alone contains elastic tissue. According to Schinz *et al.*,[18] the width of a normal adult male trachea is between 15 and 22 mm. Pohl[14] concluded from the postmortem study of his case that a congenital weakness of elastic or perhaps of the whole connective tissue system was present. However, he also felt that the effects of many years of inflammation and irritation were superimposed. The biopsy material from Rouan's[17] patient showed plasmocytic infiltration with chronic inflammation of the mucosa.

Despite the concurrence of opinion concerning the congenital origin of this condition, the role of inflammation as an aggravating factor cannot be overlooked. Cases reported previously, as well as our own, showed varying degrees and types of associated pulmonary disease, *i.e.*, bronchiectasis, bronchiolectasis, bullous emphysema, diffuse emphysema, chronic bronchitis and pulmonary fibrosis. Thus evidence of severe, chronic infection of the upper respiratory tract is present in all patients, even though most authors regard it as merely a complicating element in a disease with a primary structural defect of the tracheobronchial wall. Perhaps the best evidence against claims that tracheobronchiomegaly is acquired is its apparent rarity as compared with the wide prevalence of chronic pulmonary disease of all types.

CLINICAL ASPECTS

Tracheobronchiomegaly is manifested clinically by many signs and symptoms of chronic respiratory tract disease, but there is nothing to distinguish it from a great variety of other respiratory ailments. Symptoms include an unusually loud cough, dyspnea, hoarseness and sputum production which is often copious and purulent. Spontaneous pneumothorax and pneumonia may develop. The history is often that of long duration with onset in infancy or early childhood. The youngest patient reported to date was 8 years of age[4] and the oldest 64. Our own cases were all in the fourth or fifth decade.

BRONCHOSCOPIC FINDINGS

Bronchoscopic examination in tracheobronchiomegaly may suggest the lesion inasmuch as several observers have recorded identical findings. Mounier-Kuhn[11] found difficulty in determining the position of the bronchoscope because of the unusually large dimensions of the tracheobronchial tree. Diaz[3] observed an enormous tracheal lumen and then encountered an obstruction which could be pushed aside easily by the tip of the bronchoscope since it was merely the redundant tracheal wall in a collapsed state. Kartagener and Ulrich[8] noticed the unusual over-all width of the trachea and an even more pronounced saccular dilatation a few centimeters above the carina. He also observed the narrow lumen produced by the sagging wall which fell in a semicircle into the lumen of the trachea on expiration but which could be pushed back with very little pressure. The left main bronchus, just below its origin, widened in a saccular manner and underwent contraction and dilatation synchro-

nous with respiration, giving an impression similar to that of a dilated esophagus. Rouan[17] observed that the bronchoscope rested on a membranous wall which was falciform in contour and whose free border was almost in contact with the opposite wall of the trachea. This wall hung at a right angle from the posterior membranous

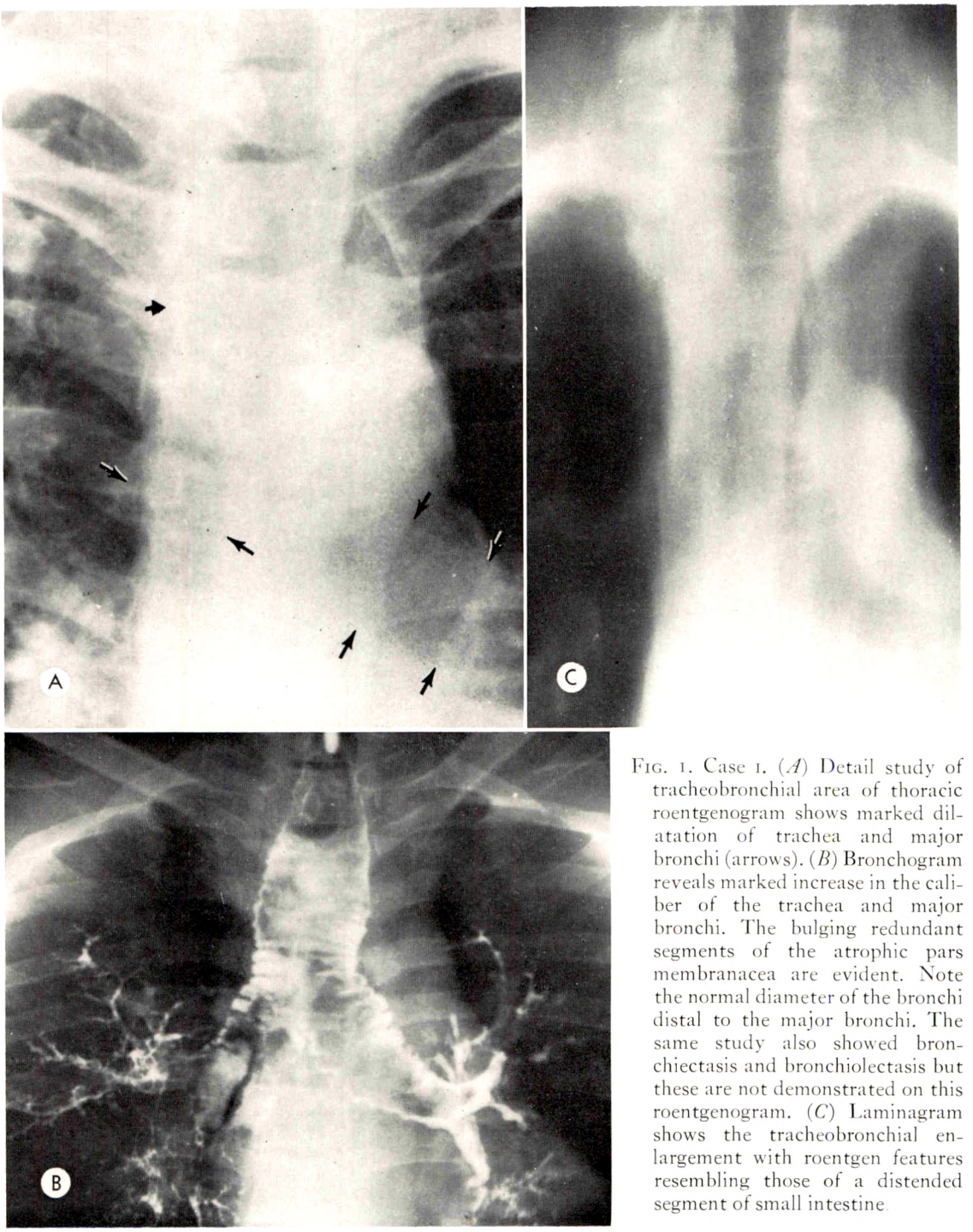


Fig. 1. Case 1. (*A*) Detail study of tracheobronchial area of thoracic roentgenogram shows marked dilatation of trachea and major bronchi (arrows). (*B*) Bronchogram reveals marked increase in the caliber of the trachea and major bronchi. The bulging redundant segments of the atrophic pars membranacea are evident. Note the normal diameter of the bronchi distal to the major bronchi. The same study also showed bronchiectasis and bronchiolectasis but these are not demonstrated on this roentgenogram. (*C*) Laminagram shows the tracheobronchial enlargement with roentgen features resembling those of a distended segment of small intestine.

wall and had to be "overcome" before the bronchoscope could be passed farther distally. He also noted that the tracheal dimensions were so vast that it was impossible to see all of the tracheal area in a single endoscopic field. He compared the capacity of the bronchoscopic light in this huge trachea to that of a "flashlight" in a tunnel, and therefore inadequate for total illumination of the large tracheal chamber. Olmer *et al.*[13] expressed surprise that their case was not detected bronchoscopically. In Case I of our series redundancy of the wall of the left main stem bronchus was noted by the bronchoscopist. In the remainder of our patients neither redundancy nor dilatation was noted on bronchoscopic examination. Bronchoscopy was not done, however, in Case III.

ROENTGEN CHARACTERISTICS

The plain roentgenogram of the chest in tracheobronchiomegaly is distinctive. Doyle *et al.*[4] found that the width of the tracheal air shadow was equivalent to that of the vertebral column. Rouan[17] also remarked upon the unusual quadrangular hyperlucency he observed in the superior mediastinum Olmer and co-workers[18] made a similar observation. In our patients the unusual size of the trachea was apparent on the plain posteranterior roentgenogram in Cases I, II, III and IV (Fig. 1*A*, 2*A*, 3*A* and 4*A*) and on the lateral view in Cases II and IV (Fig. 2*B* and 4*B*). The trachea was of normal size in Case V. The enlarged major bronchi were not distinctly evident on the plain roentgenogram in our patients with the exception of Case I. In this patient laminagraphic study demonstrated the enlarged trachea and major bronchi as well as the sac-like recesses formed by the redundant musculo-membranous tissue. This is manifested by alternate bands of air and soft tissue density which bear a striking resemblance to a dilated small intestine in which the valvulae conniventes are seen (Fig. 1*C*).

The bronchographic findings are pathognomonic, confirming the unusual width of the trachea and major bronchi and outlining the sac-like recesses, which contain pools of bronchographic contrast material.

In addition to these tracheobronchial changes, there may be a variety of abnormalities in the more distal bronchi and parenchyma. Emphysema, with or without bullous changes, or pulmonary fibrosis may be evident on the plain roentgenogram. Bronchographic studies may also demonstrate associated bronchiectasis, bronchiolectasis or chronic bronchitis.

The fluoroscopic observation of Pohl[14] during bronchography is also of great interest. He noted that the lipiodol "descended slowly and distributed itself slowly. Filling of the trachea and larger bronchi took a long time. The walls were covered more densely than usual. Eddies and currents due to mixing of air, lipiodol and secretions gave the appearance of a boiling pot . . . an appearance that is not the picture of movement and activity of the bronchial musculature but rather passive distortions due to the loss of supporting tissue."

The over-all configuration of the dilated trachea as outlined by the contrast material has been likened to that of a bottle,[11] and a sausage,[14] the latter due to the relative

TABLE I

MEASUREMENTS IN 5 CASES OF TRACHEOBRONCHIOMEGALY*

Case No.	Sex	Largest Diameter in mm.		
		Trachea	Right Main Bronchus	Left Main Bronchus
1	M	40.0	26.0	30.0
2	M	45.0	32.0	25.0
3	F	35.0	28.0	25.0
4	M	36.0	25.0	20.0**
5	M	20.0**	30.0	25.0

* Measurements were made at the largest diameter of the trachea and bronchi.

** Values less than mean plus 3 standard deviations.

narrowing of the proximal and distal trachea. The opacified, dilated major bronchi reminded Diaz[3] of "frog's legs."

EVALUATION OF MEASUREMENTS

In an attempt to determine the statistical value of the measurements obtained in our patients with tracheobronchiomegaly (Table 1), similar measurements were made in 50 consecutive bronchograms of adults (Table II). All films had been exposed at 40 inches. Comparison of the two groups

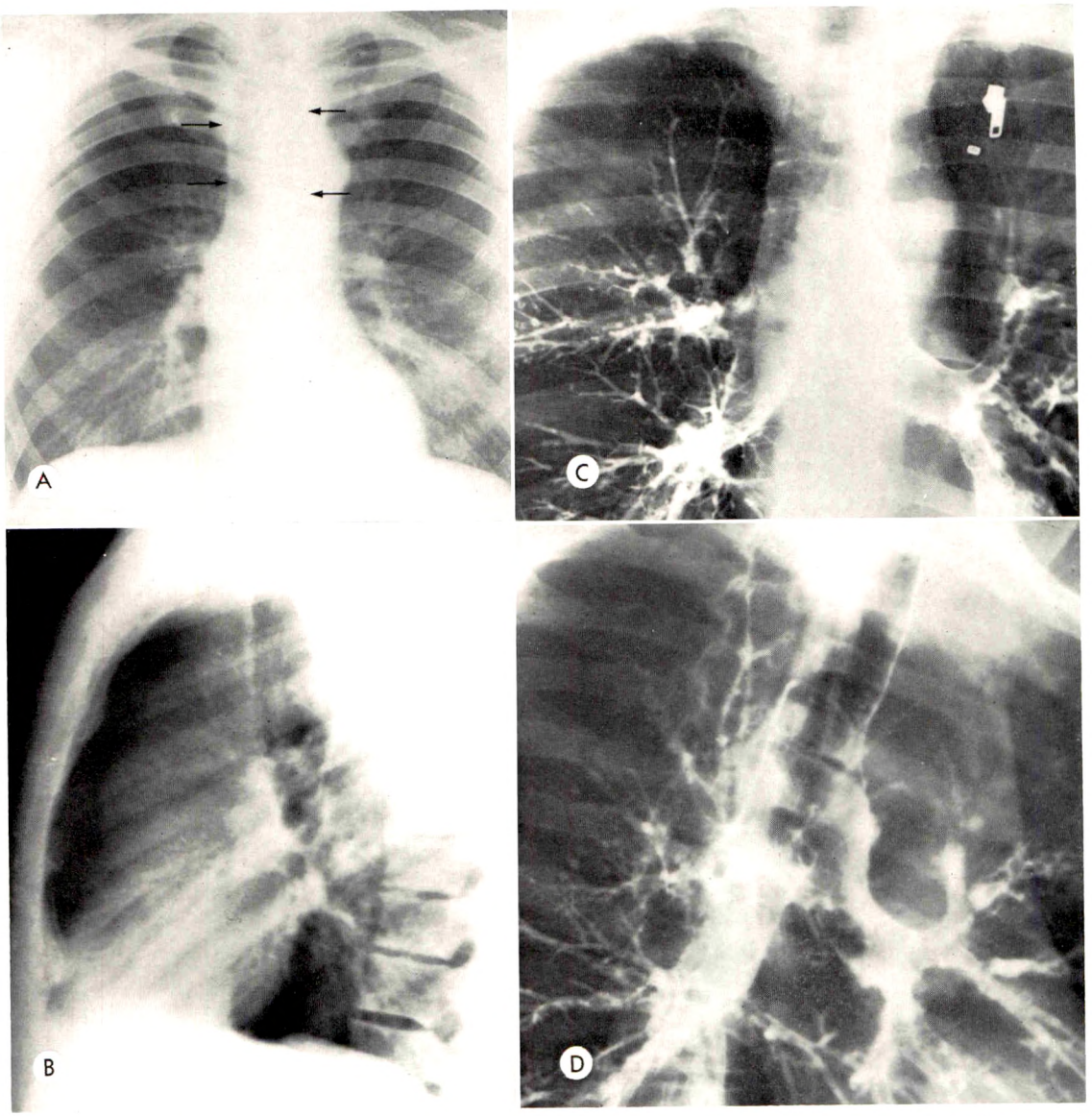


FIG. 2. Case II. (*A*) The right portion of the air column of the huge trachea projects into the right upper lung field. Its left margin is indistinctly seen, superimposed upon the left side of the thoracic spine (arrows). (*B*) The great dilatation of the trachea is well demonstrated on the lateral thoracic roentgenogram. (*C*) Bronchogram shows the huge trachea and major bronchi, distal to which there is abrupt transition to bronchi of normal size. (*D*) Right oblique view of bronchographic study demonstrates the extreme distention of the trachea and major bronchi. Changes of chronic bronchitis and bronchiolectasis are also evident.

revealed striking differences. With two exceptions, all of the measurements in the cases of tracheobronchiomegaly proved to be in excess of 3 standard deviations of the mean value of the 50 cases used for comparison (Table II).

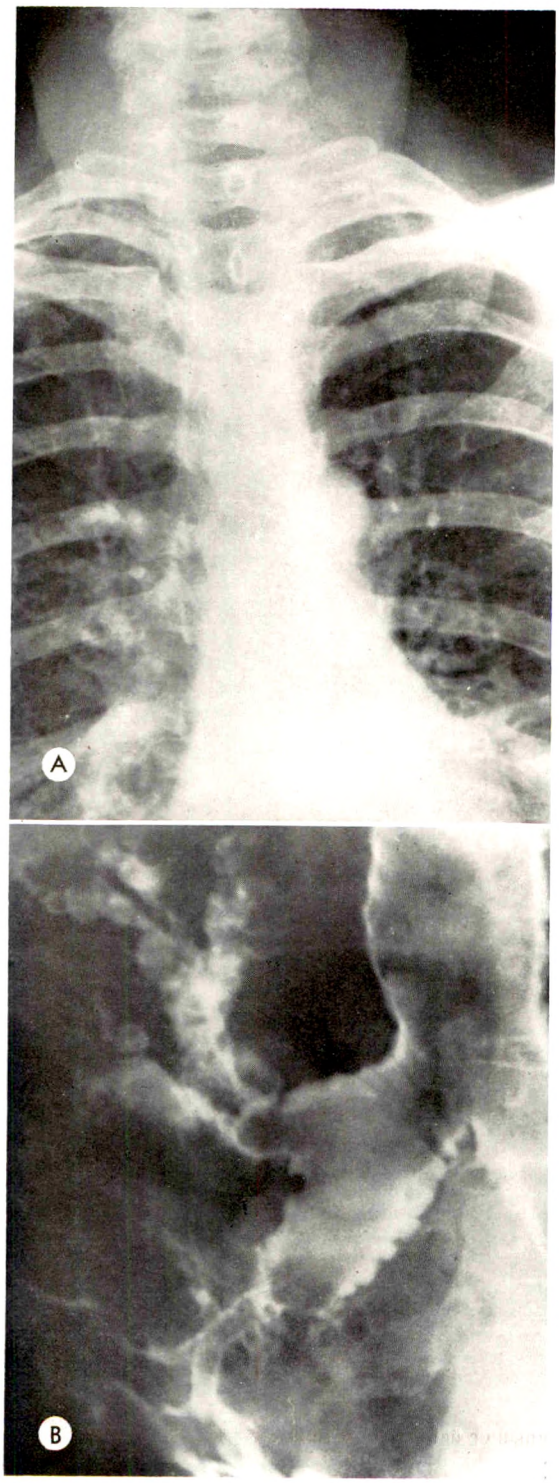


FIG. 3. Case III. (*A*) Detail view of the large tracheal air column evident in the plain roentgenogram of the thorax. Severe pulmonary fibrosis is also evident in the lung fields. (*B*) Bronchogram shows the large trachea and major bronchi. The redundant folds of the pars membranacea, manifested in the scalloped margins of the major bronchi and trachea, are also demonstrated. Saccular bronchiectasis is present in the right upper lobe.

REPORT OF CASES

CASE 1. A 35 year old white male shipping clerk was hospitalized on September 20, 1956 with the chief complaint of an upper respiratory infection of 3 weeks' duration. He had a severe cough, productive of yellowish thick sputum. His cough was extremely loud and booming in character. On occasion, the sputum was tinged with blood. He had had a chronic cough for approximately 20 years and gave a history of pneumonia in 1943 and again in 1944. He was a heavy smoker.

On examination of the chest many rhonchi were noted intermittently. The patient's testicles were atrophic and his breast tissue was prominent. He was thought to have Klinefelter's syndrome.

Serial roentgenograms of the chest revealed tracheal dilatation (Fig. 1*A*) and right middle lobe and subsequently left lower lobe atelectasis. The patient was bronchoscoped and the trachea was thought to be normal. The bronchoscope was passed with some difficulty into the left main bronchus because in expiration the posterior wall of this bronchus collapsed and obliterated the lumen. The right main stem bronchus was entered without difficulty. No intrinsic lesion was seen in the tracheobronchial tree.

A bronchogram showed marked dilatation of the trachea and bronchi which apparently was not detected bronchoscopically (Fig. 1*B*). The trachea measured 4.0 cm., the right main bronchus 2.6 cm. and the left main bronchus 3.0 cm. Changes of bronchiectasis and bronchiolectasis were also noted. A bronchogram made in 1942 showed similar changes.

A laminagram demonstrated the large trachea and major bronchi. The appearance here resembled that of a loop of distended small intestine (Fig. 1*C*).

With antibiotic therapy the atelectasis cleared and the patient was discharged. He was asymptomatic except for the booming cough.

Case II. A 39 year old white male gas station attendant was hospitalized on October 1, 1959 for a complaint of hemoptysis which had oc-

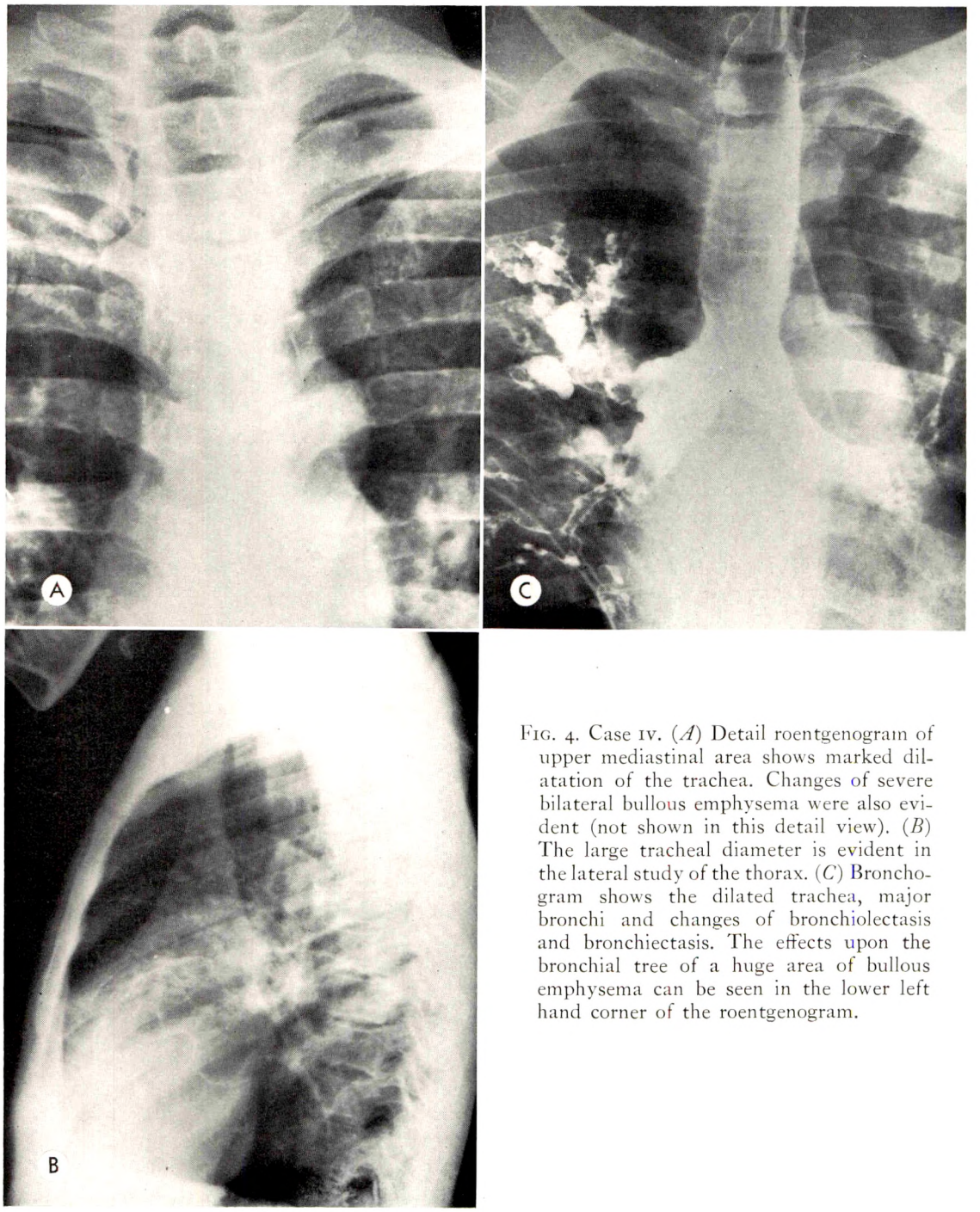


Fig. 4. Case IV. (*A*) Detail roentgenogram of upper mediastinal area shows marked dilatation of the trachea. Changes of severe bilateral bullous emphysema were also evident (not shown in this detail view). (*B*) The large tracheal diameter is evident in the lateral study of the thorax. (*C*) Bronchogram shows the dilated trachea, major bronchi and changes of bronchiolectasis and bronchiectasis. The effects upon the bronchial tree of a huge area of bullous emphysema can be seen in the lower left hand corner of the roentgenogram.

TABLE II

MEASUREMENTS IN 50 CONSECUTIVE BRONCHOGRAMS*

(Values in mm.)

	Diameter			Standard Deviation	Mean Plus 3 Standard Deviations	Standard Deviation of Largest Value from Mean
	Smallest	Largest	Mean			
Trachea	13.0	25.0	20.2	3.4	30.5	1.4
Right Main Bronchus	9.0	22.0	16.0	2.6	24.0	2.3
Left Main Bronchus	9.0	20.0	14.5	2.8	23.0	1.9

* Measurements were made at the largest diameter of the trachea and bronchi.

curred 4 days prior to admission. He gave a history of chronic cough of 15 years' duration which was productive of about 2 ounces of mucus daily. The cough would become exacerbated with upper respiratory infections. About 5 years prior to admission, he first noted hemoptysis occurring annually. At the time of his present illness, his cough was productive of about 100 cc. of thick, yellowish sputum daily. During the year prior to admission he had noted exertional dyspnea. He smoked one package of cigarettes daily.

Roentgen examination of the chest in the frontal position revealed a huge tracheal air column (Fig. 2*A*). The lateral study also demonstrated the huge size of the trachea (Fig. 2*B*).

Bronchoscopy disclosed marked erythema and edema of the tracheobronchial mucosa with copious amounts of mucopurulent secretions, more marked on the right than the left. All orifices were considered patent and no other abnormalities were noted. The bronchoscopic diagnosis was acute and chronic bronchitis with possible bronchiectasis.

A bronchogram revealed dilatation of the trachea and of both right and left main bronchi (Fig. 2, *C* and *D*). Changes of bronchiolectasis and chronic bronchitis were also noted (Fig.2*D*). The trachea measured 4.5 cm. The right main bronchus was 3.2 cm. and the left main bronchus was 2.5 cm.

The patient was treated with antibiotics and discharged as improved.

CASE III. A 39 year old Puerto Rican female was hospitalized on September 1, 1960 for existaxis of 4 days' duration. She gave a history of "asthma" associated with a chronic cough of 15 years' duration. The cough was productive of small amounts of yellow mucus.

A dilated trachea and generalized increase in the pulmonary markings, thought to represent severe pulmonary fibrosis, were evident in the plain roentgenogram of the thorax (Fig. 3*A*).

Bronchographic study demonstrated dilatation of the trachea and of both main bronchi (Fig. 3*B*). The trachea measured 3.5 cm. in its greatest diameter, the right main bronchus 2.8 cm. and the left main bronchus 2.5 cm. Bronchiectatic changes were also noted.

Bronchoscopy was not done.

A posterior nasal pack was used to stop the epistaxis and the patient was discharged on October 13, 1960.

CASE IV. A 33 year old Negro male truck-driver was first hospitalized on March 1, 1958 with the chief complaint of productive cough and increasing exertional dyspnea of 3 weeks' duration with fever of 1 week's duration. He stated that he had had pneumonia on four occasions during the preceding 9 years. In the year prior to admission, he had noted increasing susceptibility to upper respiratory infections. Exertional dyspnea had been present for the past 5 years.

Roentgen study of the chest revealed bilateral bullous emphysema and the trachea was dilated (Fig. 4, *A* and *B*). Pneumonic consolidation was present on the left. He was treated with antibiotics. Because of the marked bullous emphysema, an attempt was made to induce therapeutic pneumoperitoneum. However, an attack of syncope developed after 500 cc. of air had been injected and treatment was discontinued. He did well on antibiotics and was dis-

charged on April 11, 1958.

He was re-admitted on March 2, 1959 with the chief complaint of increasing exertional dyspnea and persistent productive cough. Treatment with antibiotics and bronchial dilators was given and he was discharged improved on March 20, 1959.

He was again admitted on April 30, 1959 with similar complaints of exertional dyspnea, cough, productive of yellowish sputum, and fever. Similar therapy was administered and he was discharged improved on May 13, 1959.

His last admission was on January 25, 1960 for similar complaints.

Bronchographic examination at this time revealed a dilated trachea that measured 3.6 cm. in its greatest diameter. The right main bronchus was 2.5 cm. and the left main bronchus 2.0 cm. (Fig. 4*C*). Bronchiolectasis, bronchiectasis and the previously noted bullous emphysema were also demonstrated.

The patient was treated medically and discharged on June 8, 1960.

Case v. A 45 year old Negro male was hospitalized on January 12, 1960 with the chief complaint of productive cough, fever and dyspnea of 5 days' duration. His cough was productive of thick, brownish-yellow mucus. He gave a history of asthma and chronic cough of 10 years' duration. He had had "double pneumonia" as a child. He smoked one package of cigarettes daily.

Plain reontgenograms of the chest revealed a left lower lobe pneumonia.

Bronchographic examination performed on two occasions showed dilatation of both main bronchi but not of the major portion of the trachea (Fig. 5). This was the only case in our series in which the diameter of the trachea was normal throughout most of its extent. However, it was wide at the carinal level, measuring 3.5 cm. Above this level the tracheal diameter was 2.0 cm. Changes of bronchiectasis were also present.

He was treated with antibiotics and after a prolonged course was discharged from the hospital on February 20, 1960.

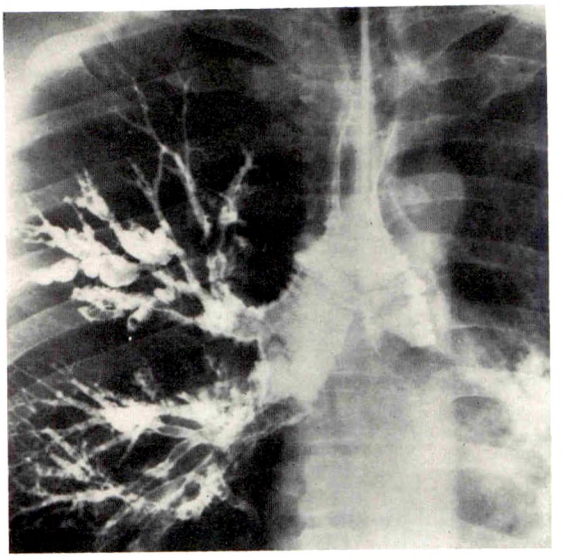


Fig. 5. Case v. Bronchogram shows severe dilatation of the major bronchi. The proximal portion of the trachea is not dilated but there is abrupt widening at the bifurcation. Bronchiectatic changes are also evident.

SUMMARY

1. Tracheobronchiomegaly (The Mounier-Kuhn syndrome) is a distinct clinico-roentgenologic entity. It is manifested by dilatation of the trachea and major bronchi and is associated with chronic pulmonary disease.

2. Plain roentgenograms of the chest in posteroanterior and lateral projections may suggest the diagnosis. Laminagraphy and bronchography are diagnostic.

3. Bronchoscopically the tracheal and bronchial lumens are abnormally spacious and the posterior membranous wall may occlude the lumens on expiration.

4. Four patients with tracheobronchiomegaly and one with bronchiomegaly alone are reported.

5. The term tracheobronchiomegaly is suggested as an appropriate designation for this disease entity.

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FIFTY-THREE CASES OF CARCINOMA OF THE BREAST, OCCULT UNTIL MAMMOGRAPHY*

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THE occult carcinoma of the breast may be defined as one which remains totally unsuspected following examination by the usual methods used to diagnose breast cancer, including an examination of the breast by an experienced and competent physician. To qualify for this definition, no symptoms (vague pain, itching or heaviness) nor signs (nipple discharge, change in breast contour, or nodules) should be present which would suggest a disease process within the organ. An alternate definition would include carcinomas on which biopsies would not be performed without a roentgenographic diagnosis of malignant disease. Patients with occult carcinoma of the breast may have some symptom referable to the breast or some sign that could possibly be associated with carcinoma but the breasts must otherwise be normal to examination. The patient may have a palpable nodule but carcinoma elsewhere in the breast is unsuspected. Any carcinoma that produces even vague palpatory findings is excluded from classification as occult. Cases of breast carcinoma fulfilling these criteria, with an unequivocal mammographic diagnosis of carcinoma, will be described.

The demonstration of unsuspected carcinoma by mammography has most often convinced clinicians of the value of this roentgenographic procedure. Most readily convinced has been the surgeon who has found a breast normal to palpation and has then explored that portion of the breast indicated by mammograms to confirm the roentgen diagnosis of malignant disease. These surgeons have helped to establish mammography as a routine examination at M. D. Anderson Hospital and Tumor Institute. Our experience has been that, initially, radiologists are more hesitant to accept mammography, because they are aware of the many previous attempts to revive soft-tissue roentgenographic techniques which have subsequently lapsed into disuse. Perhaps now that an acceptable roentgenographic technique has been developed which is simple, accurate, safe and nontraumatic (and one in which the clinician is interested), mammography will be used and perfected so that it will assume its proper place among diagnostic roentgenographic procedures.

MATERIAL

Fifty-three cases of occult breast carcinomas were seen in 2,000 consecutive breast roentgen examinations performed on 1,194 patients during the period from May, 1956, to August, 1960. These patients were referred for mammography either by the hospital breast clinic because of a palpable nodule in one breast, nipple discharge or nipple retraction, a symptom of breast disease, or by the medical service in search of an undetermined primary carcinoma. If a clinically obvious or proven carcinoma was present in one breast, it was not studied by roentgen examination. During the period of this study, 1,733 new patients were admitted to the breast clinic with lesions which were biopsied; of these, 1,315 had malignant lesions and 418 had benign lesions.

The 19 cases of occult carcinomas referred to in the previously reported group of 1,000 consecutive examinations[1] are included in this series of 53.

All patients with unsuspected carcinomas, in addition to the routine admission

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physical examination, were examined specifically for breast disease. Each mammogram was reported without benefit of history or physical findings and a code number was attached at the time of interpretation to indicate the presence of malignant disease. In all 53 cases of occult breast carcinoma, the diagnosis made by mammographic examination was subsequently confirmed by pathologic examination.

Three other cases of occult carcinoma occurred but were not included in the series because the mammograms were reviewed only in consultation. The 3 cases included: (1) a patient with bilateral mammoplasty who had a questionable nodule in one breast, with bilateral primary carcinomas found on mammography; (2) a patient who had inflammatory carcinoma of the breast, with no abnormality noted by several clinicians; and (3) an x-ray technician with an unsuspected carcinoma in one breast whom the radiologist had used to assess his roentgenographic technique; the mammograms of this patient were submitted solely for an opinion on the technical quality of the roentgenograms.

RESULTS

Table I lists the various signs and symptoms which accompanied the 53 clinically unsuspected carcinomas of the breast.

A histologic evaluation of axillary lymph nodes (Table II), available in 42 of the 53 cases, showed axillary lymph node metastasis in less than one-half of the cases. Disregarding the 11 patients sent for mammography in the presence of proven malignant disease in the axillary lymph nodes, metastasis was present in only one-third of the cases. This group of mammary carcinomas of unselected histologic types, detected by mammography prior to clinical manifestations and with a lower incidence of axillary lymph node metastasis, should have a better prognosis. These few cases, on the basis of axillary lymph node metastasis, compare with the more favorable histologic types of carcinoma: the gelatinous carcinomas with an incidence of axillary metas-

TABLE I

CARCINOMA OF THE BREAST UNSUSPECTED CLINICALLY IN A SERIES OF 2,000 MAMMOGRAMS TAKEN FROM MAY, 1956 TO MAY, 1960

No clinical signs or symptoms of carcinoma	
Previous radical mastectomy, survey of remaining breast	9
Bilateral primary carcinoma, second primary not suspected	9
Symptoms or clinical signs of benign disease in opposite breast	3
Distant metastases, primary undetermined	3
Axillary lymph node involvement, biopsy material malignant, normal breast clinically	11
No clinical signs or symptoms associated with the carcinoma	
Nipple retracted, no mass palpable	2
Nipple discharge, no mass palpable	2
Nipple erosion, no mass palpable	4
Vague complaints (cancerophobia)	3
Vague nodularity, no dominant nodule to biopsy	3
Nodule palpable, not associated with the carcinoma	4
Total	53

Note: The series included 764 lesions proven by biopsy with 431 being malignant and 333 benign. None of these carcinomas would have been biopsied without an unequivocal diagnosis of carcinoma by mammography.

TABLE II

AXILLARY LYMPH NODE INVOLVEMENT ACCORDING TO THE SIZE OF THE PRIMARY LESION IN THE 53 CARCINOMAS OF THE BREAST, OCCULT UNTIL MAMMOGRAPHY

Size	No. of Patients	Axillary Lymph Nodes		
		Histologically Negative	Histologically Positive	Histology Unknown
Less than 1 cm.	7	4	1	2
1–2 cm.	19	8	8	3
More than 2 cm.	20	7	10	3
Diffuse	7	1	3	3
Total	53	20	22	11

tasis of 43 per cent,[8] and the medullary carcinoma with lymphoid stroma with 43.4 per cent axillary metastasis.[9]

The following cases illustrate some of the situations in which mammography led to the correct diagnosis. In each instance the mammogram showed the carcinoma, and the diagnosis was reported without equivocation.

REPORT OF CASES

Case I. L.S., a 68 year old white female, was admitted with a palpable nodule in the right breast; the left breast was clinically normal but pendulous. Mammograms showed a 2.5 cm. carcinoma of the right breast and a 7 mm. carcinoma deep in the substance of the left breast. Following a right radical mastectomy for carcinoma, proven by frozen section material, a left simple mastectomy was performed. Because the carcinoma in the left breast was not palpable in the resected specimen, the pathologist was requested to examine the left breast, which after slicing he declared grossly normal. However, one surgeon, noting that some of the slices were thicker than 7 mm., requested thinner slicing. A small nodule measuring 4×6 mm. was then discovered and was histologically proved to be adenocarcinoma.

Case II. F.L., a 77 year old white female, was admitted with bloody pleural effusion containing malignant cells; the primary site of the malignant disease was undetermined. The breasts were normal to physical examination. Mammography revealed a 3 cm. invasive carcinoma (Fig. 1). The surgeon who attempted to perform a biopsy examination for histopathologic confirmation could feel only fatty tissue. After localization of the lesion from the mammograms, a second biopsy examination was performed.

Case III. L.M., a 55 year old Negro female, was examined because of a supraclavicular mass which proved to be adenocarcinoma on biopsy examination. Although the breasts were clinically normal, mammograms revealed bilateral breast carcinoma. The carcinoma in the left breast was palpable only after it was localized on the mammogram. The carcinoma in the right breast (Fig. 2) was not palpable; it is still not palpable after an interval of 23 months. Neither lesion has enlarged significantly during this time. No further metastases have developed and no treatment has been instituted. Since biopsy examination of the lesions was not done, this case is not included in Table 1.

Case IV. L.W., a 48 year old Negro female, 8 months before admission, had a right radical mastectomy for carcinoma of the breast. At the time of admission a mammogram (Fig. 3), done on the left breast as a survey, showed inflammatory carcinoma. A diagnosis of traumatic fat necrosis was made by biopsy examination. Two months later the entire breast was filled with inflammatory carcinoma with widespread slough and nodular masses of tumor growing through the biopsy site. A second biopsy examination was performed and the pathologic diagnosis was adenocarcinoma of the breast.

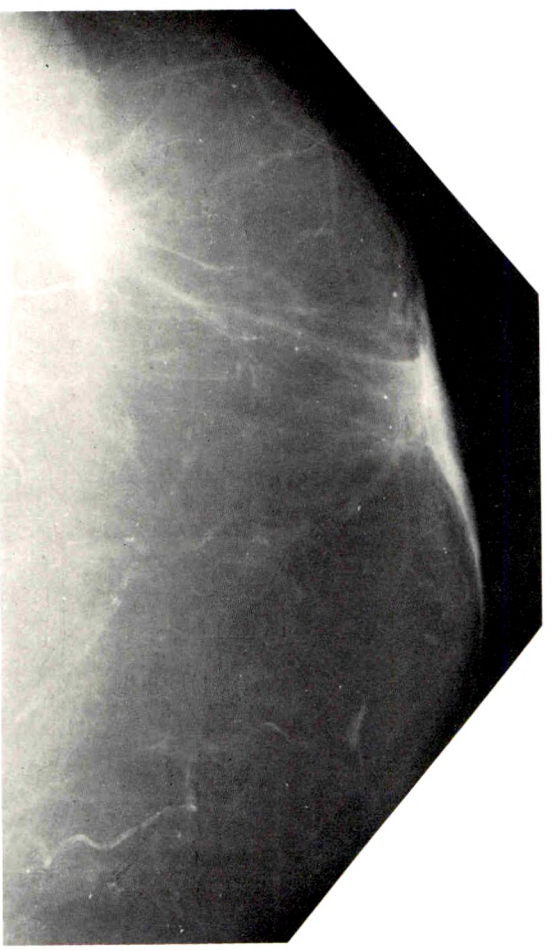


Fig. 1. Case II. Mammogram showing a 3 cm. invasive carcinoma.

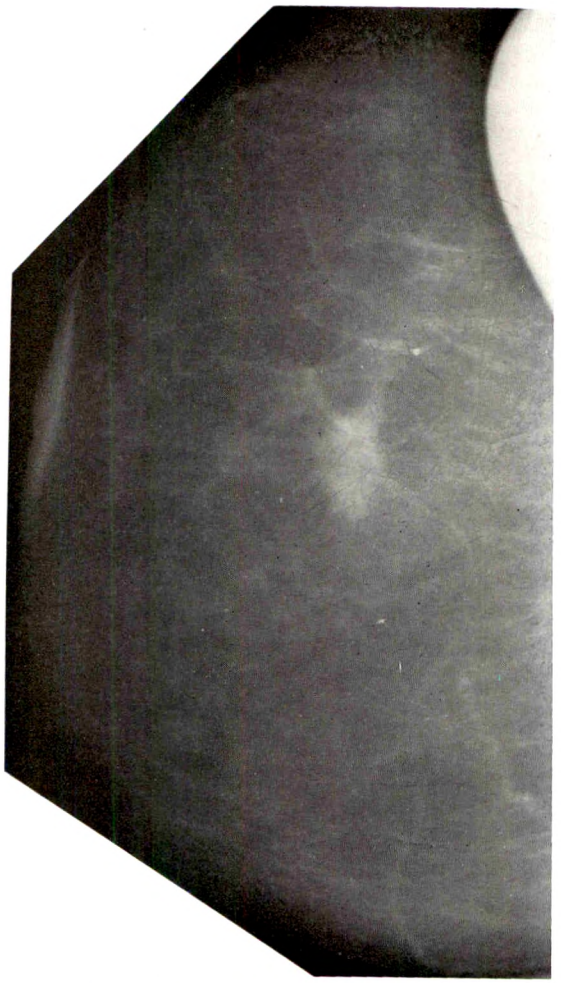


Fig. 2. Case III. Mammogram showing a nonpalpable carcinoma.

Case V. E.S., a 68 year old white female, complained of tender breasts of 3 weeks' duration with a bloody nipple discharge during the same period. Upon physical examination there was a 2×3 cm. nodule in the outer quadrant of the right breast. Mammograms on March 7, 1959, showed dilated ducts beneath the areola and 3 cystic lesions deep in the substance of the breast, one with an area of local invasion reported as carcinoma. Biopsy on March 9, 1959, showed ductal hyperplasia, intraductal papillomatosis, and sclerosing adenosis. Mammograms on September 28, 1960, showed the carcinoma to have tripled in size. On November 10, 1960, biopsy and radical mastectomy revealed the 3 lesions, one of which was an intracystic carcinoma growing through the wall of the cyst in one area and invading the breast. Although the pathologist originally thought that the intracystic papillary growths were benign, after studying the posterior aspect of the one cyst which on the mammogram showed invasion, the diagnosis of carcinoma was made.

Case VI. M.G., a 70 year old Negro female, 6 weeks prior to admission, injured her breast, with subsequent swelling. The clinicians felt that she had fibrocystic disease without a dominant nodule. A mammogram indicated the presence of a carcinoma. Following biopsy examination, the frozen section material was reported as benign; on permanent sections a diagnosis of carcinoma of the breast was established histopathologically.

Case VII. L.T., a 48 year old white female, was seen with a lesion in the medial quadrant of the right breast. She first noted the mass following an injury 18 months before admission. Mammograms revealed a 1.5 cm. carcinoma in the axillary portion of the breast. Biopsy material of the medial quadrant mass was normal; however, the area indicated on the mammograms (the axillary portion of the breast) was explored and carcinoma was found.

Case VIII. B.B., a 56 year old white female, complained of pain in the right breast of 7

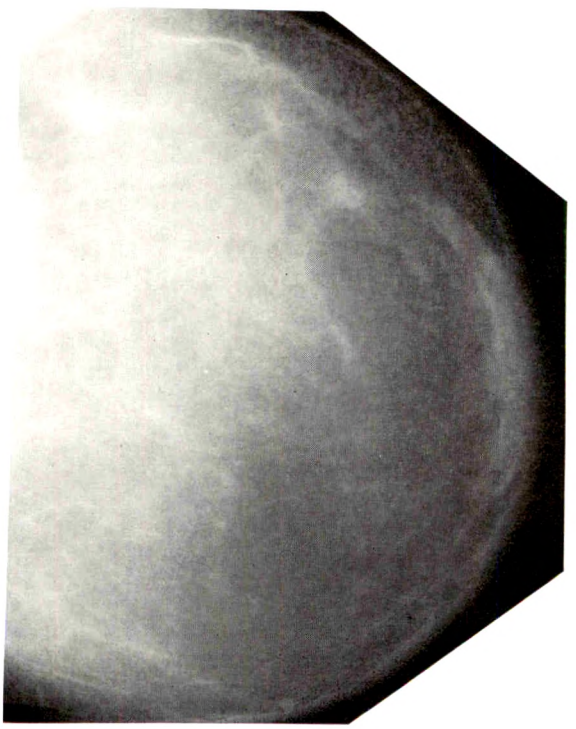


Fig. 3. Case IV. Mammogram showing an inflammatory carcinoma.

months' duration; a mass was palpable. The left breast was normal. Mammograms revealed a normal right breast but 3 foci of carcinoma in the left breast. At biopsy, the mass in the right breast was found to consist of normal breast tissue. The mammogram report had not been noted prior to surgery. The patient returned 14 months later still complaining of discomfort in her right breast; at this time both breasts were clinically free of disease. Re-examination of the breasts by mammography showed the right breast to be normal but the 3 carcinomas in the left breast had doubled in size. After the surgeons were convinced that the markers on the roentgenograms properly identified the breasts, exploration of the left breast was carried out and the diagnosis of 3 foci of carcinoma of this breast was established.

Case ix. L.B., a 44 year old white female, was admitted with a palpable nodule in the breast. Mammograms revealed a 5 cm. benign cyst, but deep to the cyst was a 1 cm. carcinoma. The surgeon was immediately alerted to the presence of the carcinoma. Upon removal of the cyst, the surrounding breast tissue was normal to palpation. The surgeon commented that "without mammography the carcinoma would have been missed, but I remembered the exact relationship of the carcinoma to the cyst and it was simple to find the small carcinoma by proceeding with sharp dissection of that area of the breast indicated by the radiologist."

Case x. J.G., a 47 year old white female, had an axillary mass that, after biopsy examination, was histopathologically diagnosed as lymphoma. The axilla was irradiated. One year later, because of a discussion as to whether irradiation of the axilla would cause diffuse skin thickening of the breast, mammograms were made which showed no skin changes but revealed a 2 cm. carcinoma deep in the substance of the breast. Biopsy material indicated carcinoma of the breast. After review of the previously removed axillary tissue, the histopathologic diagnosis was changed to carcinoma of the breast with metastasis to axillary lymph nodes.

Case xi. M.S., a 55 year old white female, was admitted with a palpable nodule in the right breast and a normal left breast. Mammograms demonstrated a primary carcinoma in each breast. The right breast lesion was biopsied and diagnosed as a benign process. Two weeks later, when the surgeons explored the left breast, a frozen tissue diagnosis of benign disease was made. Because of the mammogram and clinical judgment, bilateral simple mastectomy was done. The diagnosis on the basis of the permanent sections was carcinoma of the left breast. Upon review of the tissue sections, the right breast also was seen to contain carcinoma.

DISCUSSION

Only once did the surgeon delay exploring a breast in which there was a roentgen diagnosis of carcinoma unconfirmed by clinical evidence (Case viii). This was an oversight, rectified by a surgical investigation as soon as the roentgen diagnosis of the 3 carcinomas became known. Such an attitude indicates that clinicians are relying upon mammography to reveal breast carcinomas before they become clinically evident. To date only one breast has been explored on the basis of the roentgen diagnosis for unsuspected carcinoma that did not prove to be malignant. In this case, the pathologic diagnosis was carcinoma *in situ* and a simple mastectomy was done.

Cases i, iv, v, x, and xi illustrate that mammography can be of help to the pathologists as well as to the clinician in detecting the clinically unsuspected carcinoma. Case i indicates the necessity for a more careful search through the gross specimen. In such cases, roentgenograms of the specimen are valuable in locating the small carcinoma in the pendulous breast. If the pathologist is unaware of a primary lesion in the breast producing skin thickening (Case iv), tiny foci of carcinoma in the skin may be overlooked. The wrong portion of an intracystic lesion may be studied by the pathologist unless he is aware of its invasiveness in a limited area, as shown by mammographic study of its entire periphery (Case v). The axillary lymph node containing tumor may be misleading to the pathologist if the presence of a carcinoma in the ipsilateral breast is unsuspected (Case x). Evaluation of breast lesions may present a perplexing problem to the pathologist; for example, in Case xi biopsy of the second breast would not have been performed had it not been for mammography. Only after a diagnosis of

carcinoma was established in this breast was the first breast tissue restudied and the diagnosis of bilateral carcinoma established.

The clinical material at a tumor institution varies from that of a general hospital or that in private radiology practice. Malignant disease of some type (not necessarily breast) is usually suspected. The patients are often older, with breasts more easily examined by mammography. A higher incidence of pathologic breast lesion is expected in such a group of patients. But, by the use of mammography, unsuspected carcinomas are discovered in the more general population, as reported by Martin *et al.*[7] Their series of 28 carcinomas diagnosed by mammography included 15 unsuspected lesions. Lindell and Boyle,[5] also using the same mammography technique developed at this institution, reported 4 clinically unsuspected lesions of 34 carcinoma cases. Such a yield of unsuspected breast carcinomas does not imply the use of mammography as a screening procedure for carcinoma of the breast, but these reports do indicate that mammograms of good technical quality can demonstrate carcinoma in a breast that is clinically free of the disease. Gershon-Cohen *et al.*[2] recently reported periodic mammographic examination of the breast at 6 month intervals among 1,312 women over a period of 5 years. Six nonpalpable malignant tumors were detected.

As appealing to the clinician and rewarding to the radiologist as the demonstration of an unsuspected carcinoma of the breast may be, mammography has other valuable uses. Case IV illustrates its value in treatment planning. Such lesions with diffuse skin thickening do poorly surgically; the added information from mammography may enhance selection of patients for radical mastectomy. In Case X, mammography might have aided greatly in treatment planning.

The natural history of carcinoma of the breast has not been thoroughly elucidated. Patients' histories are inaccurate. A lesion removed for microscopic study cannot be reimplanted to study its course, and a lesion partially removed for histologic examination has been unavoidably disturbed. The detail of structures on the mammograms allows close observation of a lesion and its undisturbed relationship to surrounding tissues and the entire breast. It also permits repeated study without interfering with its growth pattern.

Carcinoma of the breast in the female is the most common form of cancer and is more frequent than the combined total of malignant disease of the female generative organs.[6] Approximately one-fourth of the lesions are inoperable by current criteria, and a high percentage of those which are operable metastasize within 10 years. The 10 year survival rate becomes much higher if no involved axillary lymph nodes are found in the radical mastectomy specimens. The absolute 10 year salvage rate for patients with carcinoma of the breast in various series ranges from 18 to 33.4 per cent.[4]

The accessibility of the breast lends itself to physical examination; refinements in methods of inspection and palpation over the past 25 years have been emphasized without a corresponding increase in the salvage rate of patients with breast carcinoma. The Minnesota Cancer Detection Study, employing usual diagnostic facilities, demonstrated a 77 per cent increase in detection of all types of carcinoma but only a 6 per cent increase in breast carcinoma.[10] When a patient with breast carcinoma finally consults her physician, the chances are 1 in 4 that he will miss the diagnosis.[4]

Neither more extensive surgery nor improved irradiation, alone or combined, with or without chemotherapy, offers hope of any dramatic improvement in the 10 year survival rate for patients with carcinoma of the breast. The incidence of breast carcinoma in white females is 48.1 per 100,000 in the 35 to 39 age group; 145.7 per 100,000 in the 55 to 59 age group; 185.8 per 100,000 in the 65 to 69 age group; and 454.3 per 100,000 in the 85 and over age group. With

mammography the accuracy of a diagnosis of malignant disease increases with the age of the patients. The average life span of women continually increases.

CONCLUSION

With our present knowledge of carcinoma of the breast, it becomes apparent that an increased salvage depends upon a more accurate method of detection of carcinoma of the breast. The method should detect carcinomas that are not palpable, present no clinical signs, and cause no symptoms. Such a method should be simple, safe, inexpensive and nontraumatic. There should be no deterrent factors to women, such as prolonged history-taking and physical examination, concern over excess radiation, or concern over expensive hospitalization or surgical procedures.

Such a method may now be available. Mammography has been used to reveal carcinomas of the breast in a stage of development when the growth presented no signs and caused no clinical symptoms.

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CLINICALLY UNSUSPECTED CARCINOMA OF THE BREAST*

A STUDY IN PRIVATE PRACTICE

By JOHN E. MARTIN, M.D., JAMES M. KEEGAN, M.D., LESLIE L. LEMAK, M.D., *and* CHARLES W. YATES, M.D.
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IN DECEMBER of 1960, Egan[1] reported the findings of some 19 unsuspected cases of carcinoma in a series of 1,000 mammograms. We approached this procedure with some skepticism because of previous experience in mammography. After reviewing his 1,000 cases, we felt that with his method mammography may well have been perfected to the point where its application to the female population in general had become feasible. A similar study in private practice appeared warranted. We found the application of Egan's technique to our offices to be easy and, with the support of many local physicians, have performed within the past 8 months mammographies on 571 patients. This has given us experience enough to evaluate the place of mammography in the diagnosis of carcinoma of the breast.

For the main part the types of cases referred to us were those with diagnostic problems, involving: (1) questionably palpable masses; (2) patients who have had multiple biopsies; (3) routine scouting examinations; and (4) patients with cancerophobia. We know of only 2 cases in our group in which the surgeon was "positive" that the patients had carcinoma prior to mammography. The other carcinoma cases that we found were either unsuspected or the clinical examination was equivocal.

Table 1 shows the total number of mammographic examinations in this series, as well as the total number of biopsies and the reported pathologic diagnoses. Because so many of the patients have not been biopsied, a true estimate of the accuracy of this method of examination is not feasible. However, one significant figure is noted;

TABLE I

STATISTICAL DATA OF PATIENTS EXAMINED FROM DECEMBER, 1960 THROUGH JULY, 1961

Total No. of patients having mammography	571
No. of patients with breast biopsies	146
No. of patients with benign breast lesion	117
No. of patients with carcinoma	28
No. of patients with unsuspected carcinoma	15

that is, that 15 clinically unsuspected carcinoma cases were found. Upon beginning this series, remembering one of the fundamentals of medicine that disease processes, and especially carcinomas, have a better prognosis if diagnosed and treated early, we felt that if we could find one unsuspected carcinoma of the breast within a year, it would be worth the effort put forth. To have found 15 is particularly rewarding.

It is the purpose of this report to evaluate these 15 clinically unsuspected carcinomas. We have arbitrarily placed them into three categories.

CLINICALLY UNSUSPECTED CASES OF CARCINOMA

GROUP I

This is the asymptomatic group. These are the patients with no particular clinical findings and no palpable masses, who were examined as part of a routine physical examination, or on follow-up because of previous mastectomy. Four of the clinically unsuspected carcinomas were found in this asymptomatic group.

CASE 1. (Fig. 1). A white female, aged 73 years, had had a radical mastectomy 6 years

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Fig. 1. Case 1. Small 3 mm. medullary carcinoma deep within the outer quadrant.

previously. Routine examination of the remaining asymptomatic breast revealed a 3 mm. carcinoma. At surgery, the lesion could not be palpated so the entire quadrant of the breast was removed. (With the speciman in hand, and slicing thin sections at surgery, the pathologist took approximately 10 minutes to find the carcinoma.) There was no lymph node involvement present in the axilla.

Case II. (Fig. 2). A 57 year old white female purchased a new brassiere and felt a small mass in her right breast, which was not palpated by 3 surgeons. Mammography demonstrated a malignant lesion within 2 cm. of the skin surface of the inferior border of the breast which measured some 25 mm. in diameter. There was no lymph node involvement present in the axilla.

Case III. (Fig. 3). A 79 year old white female had had a radical mastectomy 10 years previously. Routine examination of the remaining

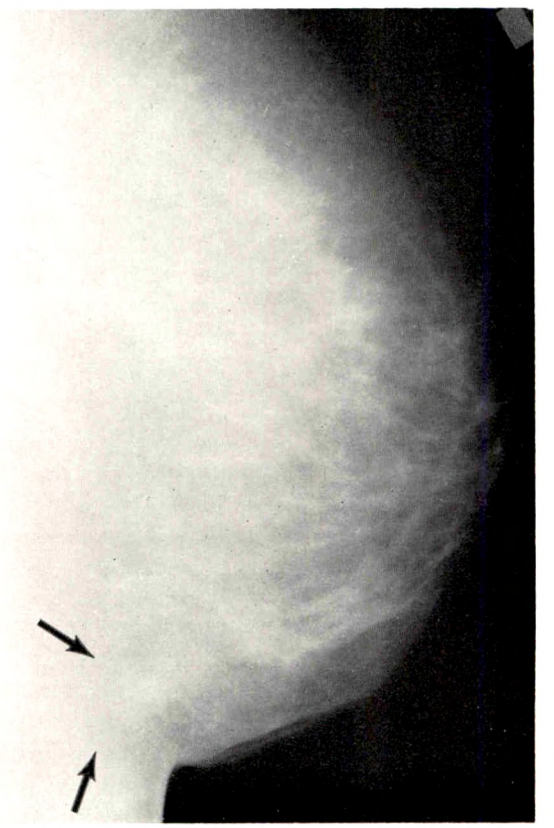


Fig. 2. Case II. Prominent scirrhous carcinoma in the inferior outer quadrant of the breast with associated skin thickening. The lesion was not palpable.

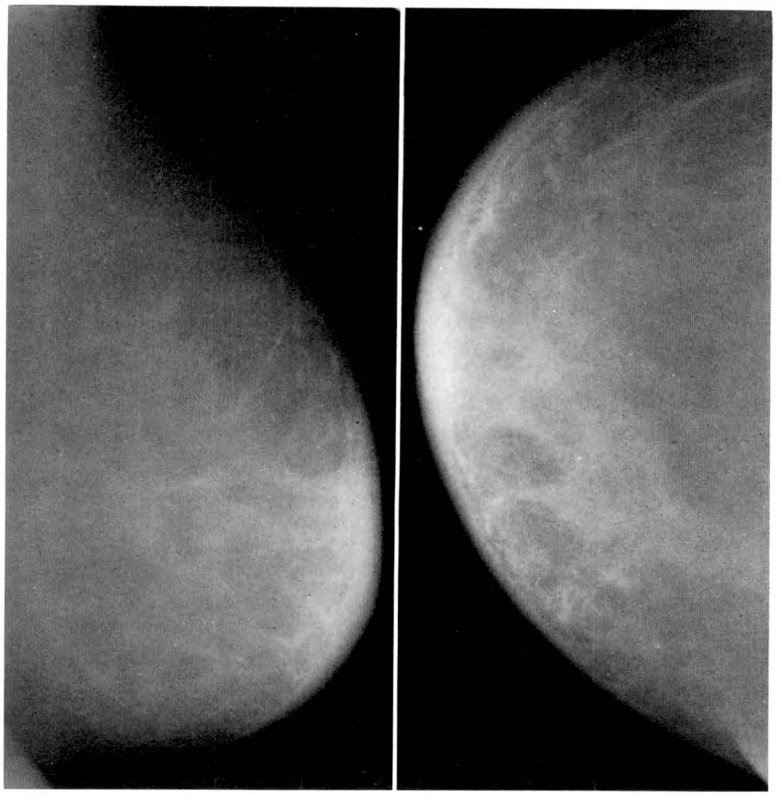


FIG. 3. Case III. Marked thickening of the skin, diagnostic of inflammatory carcinoma. Malignancy was not found clinically.

breast clinically showed a small nodule with some surrounding redness, but no clinical signs of malignancy were present. Mammography demonstrated an inflammatory carcinoma of the breast. The surgeon was reluctant to biopsy this breast. Upon biopsy, the frozen section revealed adenocarcinoma and a radical mastectomy was done. The final report was inflammatory carcinoma of the breast.

CASE IV. A 39 year old Mexican female was being treated with antibiotics for acute mastitis of two weeks' duration. Because of the poor response, mammography was done which revealed an inflammatory carcinoma.

GROUP II

This group included the patients with palpable masses in which no dominant lesion was evident. Also included were the patients with diffuse fibrocystic disease, with the so-called "knotty" breast, without a particular area which might be suspicious of carcinoma. Five of the clinically unsuspected carcinoma cases were found in this group.

CASE V. (Fig. 4). A 54 year old white female was examined as part of a routine physical examination. The referring doctor thought that this patient had fibrocystic disease. A small carcinoma was visualized on the mammogram. The surgeon was reluctant to operate, but did so on the basis of the mammographic findings, which were confirmed at surgery.

CASE VI. (Fig. 5). A 50 year old white female felt masses in her breasts and was unusually nervous. Her referring doctor had mammography performed as a matter of alleviating anxiety, and a large intraductal carcinoma was found.

CASE VII. A 56 year old white female with multiple masses in the breast was suspected by the surgeon as having fibrocystic disease. A

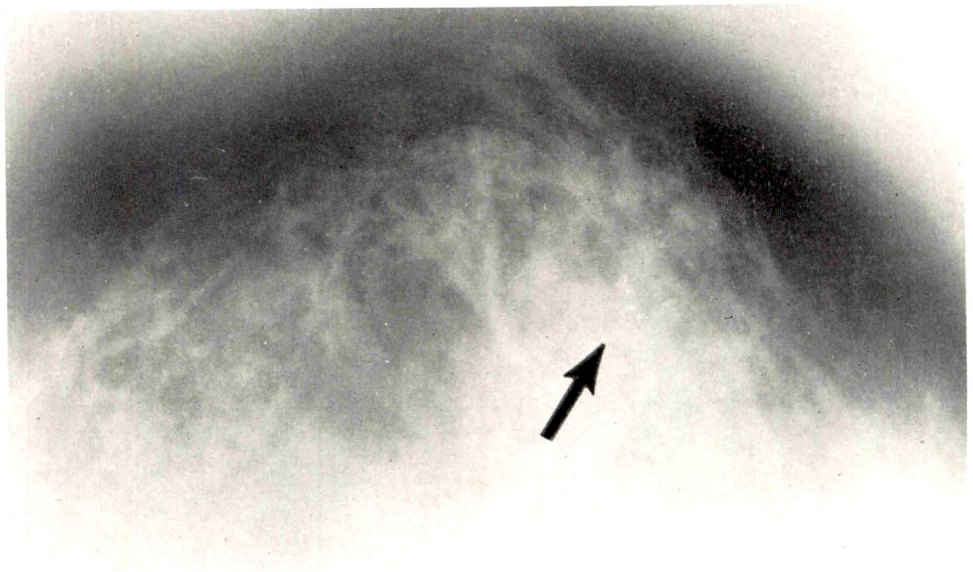


Fig. 4. Case v. Typical calcification of slow growing medullary adenocarcinoma.

mammogram demonstrated a carcinoma measuring 3 cm. in diameter.

Case viii. A 50 year old white female felt a fullness in the breast but no palpable masses were found by her physician. Mammograms showed carcinoma.

Case ix. A 62 year old white female was referred by a gynecologist to a surgeon who examined her and told her to return in 3 months. He did not feel that breast palpation revealed anything of significance. The following day, the patient had mammography done at her own insistence by referral from another physician. This disclosed a carcinoma, which was confirmed at surgery.

GROUP III

This group includes patients with a dominant breast lesion in which mammography revealed the carcinoma to be in another segment of the same breast, or in the opposite breast. Six of our patients with carcinoma are included in this particular group.

Case x. (Fig. 6). A 47 year old white female was referred because of a mass in the left breast, but a mammographic diagnosis of inflammatory carcinoma in the opposite right breast was made. At surgery, histologic diagnosis of adenocarcinoma was made. A radical mastectomy was done and the final pathologic sections were reported as pre-inflammatory carcinoma of the breast.

Case xi. A 41 year old white female was clinically suspected of having a carcinoma of the breast. At surgery, two frozen sections were taken from the suspected area and were negative. The surgeon re-read the mammography

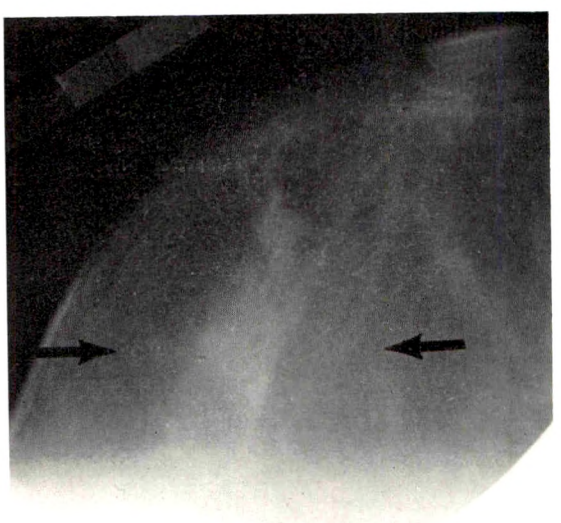


Fig. 5. Case vi. Large intraductal carcinoma of the slow growing type with calcification and associated skin thickening.



FIG. 6. Case x. Thickening of the skin of the right breast, but not of the left, diagnostic of inflammatory carcinoma.

report and found that a carcinoma was noted in another area of the breast; here a positive diagnosis was obtained.

CASE XII. A 48 year old white female was seen by an internist who felt a mass under the surface of the skin which he thought was a small cyst. The surgeon and gynecologist concurred in this clinical impression. Mammography revealed a small cyst and also carcinoma in another area of the breast.

CASE XIII. A 48 year old white female was referred because of a mass in the left breast. A small carcinoma measuring approximately 3 mm. in diameter was found on mammography immediately below the nipple area of the right breast. The lesion still could not be palpated. Surgery was delayed for 8 months, in which time the tumor increased 1 mm. in diameter and was still not palpable. At this time surgery confirmed the diagnosis.

CASE XIV. A 60 year old white female was examined by the same physician over a period of 4 years. His impression was that the patient had a sebaceous cyst of the breast. Mammography was performed upon the insistence of the patient and a large carcinoma was found in the area of the suspected cyst.

CASE XV. (Fig. 7). A 53 year old white female had a mass in her breast of 4 years' duration. The patient was examined regularly by 4 doctors, all of whom felt that this was not significant. Mammography was ordered for completeness of a yearly examination, and a carcinoma was found. The surgeon did not feel that the mass was clinically malignant.

INDICATION FOR MAMMOGRAPHY

Mammography is a diagnostic procedure which has proved of value. The following are indications for its performance:

1. In the presence of a questionable lesion of the breast which is clinically equivocal.

2. As a means of evaluating all of the breast tissue prior to surgery in the presence of a dominant lesion, clinically sus-

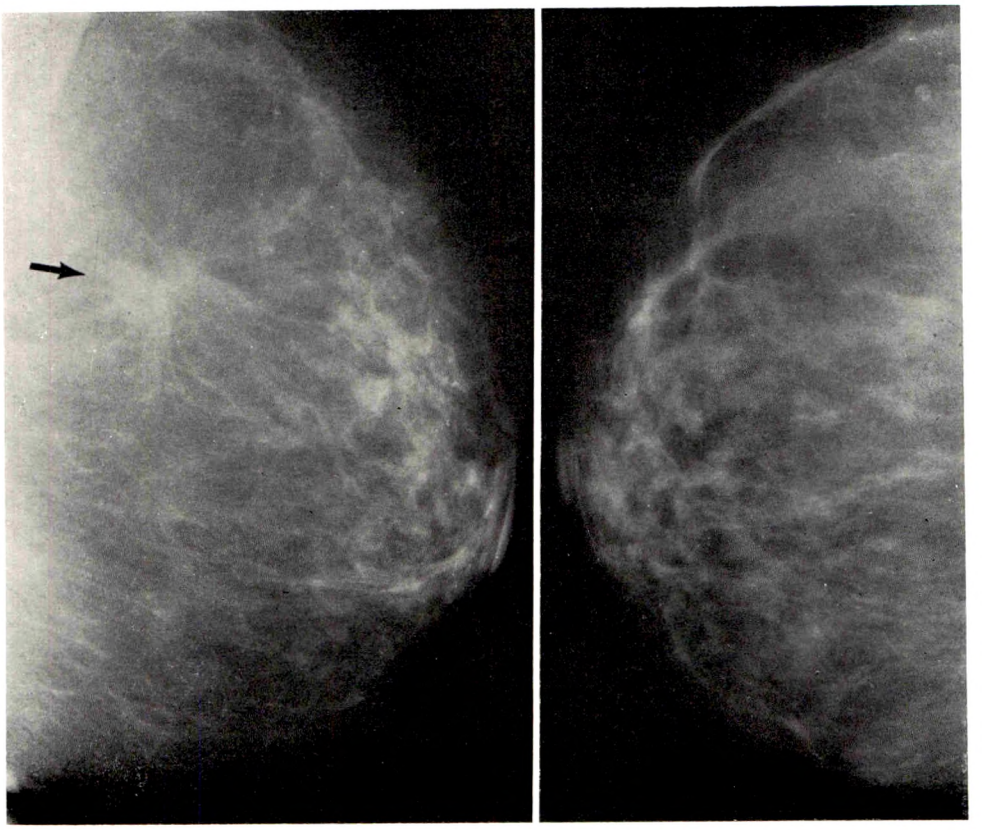


Fig. 7. Case xv. Large scirrhous carcinoma with the typical star-burst pattern.

pected of being carcinoma. In several of the cases listed, it is evident that the suspected lesion turned out to be benign, both roentgenographically and pathologically; however, a carcinoma was found in another portion of the same breast or in the opposite breast.

3. As a method of evaluating patients with a history of multiple biopsies in which the surgeon is reluctant to do further biopsy. The surgeon can thus obtain a permanent record or map of the masses of the breast. Mammography can then be performed at a future date for further evaluation and comparison.

4. To relieve anxiety in patients with cancerophobia.

5. As a safe screening procedure in women.

6. As a routine follow-up procedure at 6 to 12 month intervals of the remaining breast of patients with previous radical mastectomies.

7. In patients with metastatic disease in which the primary lesion is obscure. Initial examination by means of mammography may save many other diagnostic procedures.

DISCUSSION

Mammography should not be accepted as an absolute diagnostic method for evaluation of the female breast, but only as a diagnostic aid as part of the clinical evaluation of the patient. Its greatest value is in cases where the roentgenographic findings are definitely positive; however a negative report does not rule out carcinoma. In 5 of the 28 carcinoma cases on which mammography was performed, the diagnosis was not accurate. It is of interest to note that all of these 5 patients had clinically palpable dominant lesions. The greatest problem in

evaluating these particular patients was a marked increase in the density of the breast due to fibrocystic disease and adenosis. If primary or secondary roentgenographic signs of malignancy were present, they could not be identified through the great mass of breast tissue. As a result of these failures, we strongly urge biopsy of a dominant lesion; in all cases of adenosis; and in all unusually dense breasts. Clinical evalution and mammography should be used together so as to increase the physician's accuracy in the diagnosis of breast carcinoma.

SUMMARY

In a study of 571 patients, 15 unsuspected cases of carcinoma of the breast were discovered after mammography, demonstrating the importance of this examination as a diagnostic aid for the armamentarium of the physician. Most significant is the fact that totally unsuspected cases of breast carcinoma were found.

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INFLAMMATORY CARCINOMA OF THE BREAST*

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AS OUR experience in mammography increases, we have found it helpful not only to gather over-all statistics but also to attempt to correlate roentgen criteria in the light of established pathologic changes. Again, it is most important to emphasize that mammography does not take the place of microscopic diagnosis, but that it still functions as an important aid and we find it a worthwhile procedure in specific types of breast pathology.[2] Mammography has been well established as an important diagnostic aid in deep-seated intraductal carcinomas[5] since it does permit the diagnosis of these lesions before they are palpable, thereby permitting a higher percentage of cures. We would like to present our experience with mammography in reference to inflammatory carcinoma, not so much because it would appear to be capable of appreciably affecting the very grave course of events in this acute type of carcinoma, but rather to emphasize that it does permit one to make a fairly definite diagnosis. And above all, mammography may aid in the avoidance of the usual procrastination that frequently occurs because the process is regarded clinically as a benign inflammatory one.

MATERIAL

We have performed mammography on 12 cases of inflammatory carcinoma out of 654 studied carcinomas of which 604 were surgically proven. This incidence of 2 per cent is about the same as the 1.7 per cent reported by Barber *et al.*[1] from the Mayo Clinic.

SIGNS AND SYMPTOMS

A palpable mass or a diffuse sense of induration and firmness is almost invariably present. Seventy per cent of our cases presented a palpable dominant mass which was quite extensive and large in size. In 30 per cent, we noted a firm indurated feeling of practically the entire breast, yet without a locally dominant area. Pain and swelling of the breast are also very frequent findings; 92 per cent of our patients presented with both. The sense of tenseness and swelling tends to be more prominent with the patient standing or sitting. Redness and edematous thickening of the skin, described as "peau d'orange" (orange peel), is a most characteristic sign. Haagensen[4] in his classic text on the breast insists that one must have enlargement of the breast accompanied by both redness and edema of the skin, each involving at least a third of the entire breast, before regarding the individual as a clinical picture of inflammatory carcinoma. All of our patients presented with redness and swelling of the involved breast. Almost invariably by the time the patient presents herself, there are palpable lymph nodes. Ninety-two per cent of our patients had evident clinical involvement of the axilla.

PATHOLOGY

Grossly, the skin is thickened and edematous. Ulceration does not generally occur nor is there fixation of the skin. There is almost invariable involvement of the axillary lymph nodes. The left breast is more frequently involved than the right.

Subepidermal lymphatic blockage by tumor cells is the single diagnostic microscopic feature and, if enough sections are taken, will be noted in probably 100 per cent of all cases.[6] This finding actually accounts for the characteristic physical and clinical findings of skin thickening and edema, increase in breast size and painful

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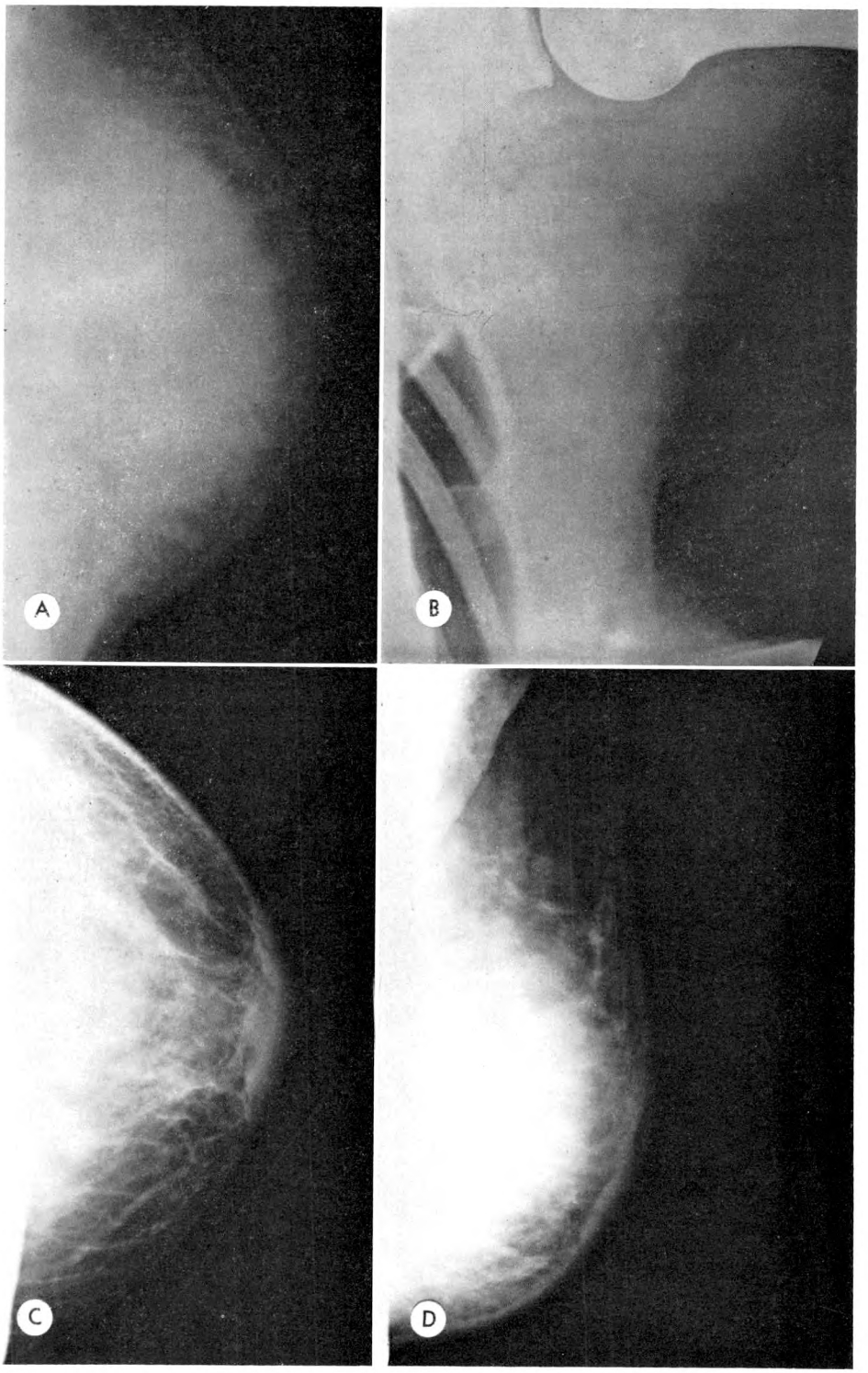


Fig. 1. Case 1. (*A*) Involved left breast. There is subcutaneous thickening, lymphatic prominence and overall increased tissue density when compared to the normal right breast (*C*). (*B*) The left axilla revealing numerous large lymph nodes. (*C*) The normal right breast. (*D*) The right breast, two months after *C* was made, now has subcutaneous thickening, lymphatic prominence and striations of increasing density consistent with a diagnosis of inflammatory carcinoma.

swelling. True inflammation does not exist. There is perivascular deposit of some lymphocytes and monocytes which is believed to be secondary to the lymphatic blockage. Using Broder's classification, most of these are in Grade IV. There is nothing characteristic in the individual cell nor in the architecture of the growth. It is merely in the manner of spread that this carcinoma manifests its individuality. Rather than growing as a direct infiltrating mass, it disseminates itself through the lymphatics. When the pathologist notes this microscopic finding in an individual who has the clinical requirements described by Haagensen, then and only then is the diagnosis of inflammatory carcinoma justified. Several cases are presented here in order to emphasize the usual roentgen and clinical features of this entity.

REPORT OF CASES

Case I. C5638. L.L., a 56 year old Negro female, had swelling, firmness and pain of the entire left breast for a period of 7 months. There was slight discoloration of the skin which had an orange peel appearance and consistency. This breast was strikingly larger than the opposite and normal breast. There were hard fixed palpable lymph nodes in the left axilla. A mammogram (Fig. 1*A*) revealed a symmetrically dense left breast with slight generalized subcutaneous thickening and prominent fine streakings beneath the skin which are believed to represent the subcutaneous lymphatics filled with cancer cells. There was no dominant or discrete mass. A mammogram of the left axilla (Fig. 1*B*) revealed numerous large lymph nodes. Examination of the right breast (Fig. 1*C*) showed it to be normal.

Surgery consisted of biopsy of the skin and dissection of one of the axillary lymph nodes. The striking finding was the presence of extensive blockage of the subcutaneous lymphatics with cancer cells consistent with the diagnosis of inflammatory carcinoma. The lymph nodes from the left axilla were involved by metastatic cancer. Treatment consisted of cobalt 60 teletherapy.

Two months later the right breast became tender, enlarged and reddened. No dominant mass was palpated. Roentgen examination (Fig. 1*D*) revealed striking changes when compared with the mammogram made two months previously (Fig. 1*C*). The over-all increase in breast density, subcutaneous thickening and lymphatic prominence justified a diagnosis of probable involvement of the right breast by inflammatory carcinoma. Cobalt 60 teletherapy was instituted to the right breast without a tissue biopsy.

Case II. C5127. C.M., a 45 year old white female, had enlargement, redness, increased firmness and pain in the left breast of one month's duration. No discrete mass was palpable. A roentgenogram (Fig. 2*A*) revealed the entire left breast to be markedly dense and a locally dominant infiltrate was not visible. The slight but definite thickening of the subcutaneous tissue and the prominence of the lymphatics in the subcutaneous area suggested a diagnosis of inflammatory carcinoma. These changes were especially evident when compared with the normal right breast (Fig. 2*B*).

A biopsy was done and disclosed the characteristic microscopic finding of subepidermal lymphatics filled with cancer cells. A radical

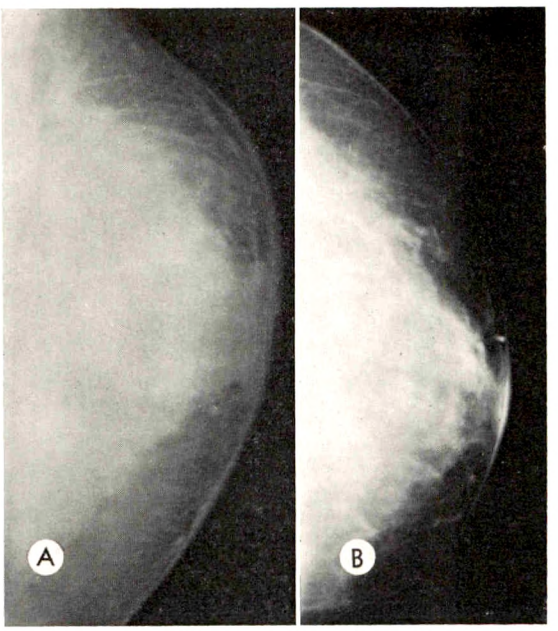


Fig. 2. Case II. (*A*) The left breast. There is subcutaneous thickening, lymphatic prominence perpendicular to the skin surface and over-all increased tissue prominence when compared to (*B*) the normal right breast.

mastectomy was performed and most of the axillary lymph nodes were found to be involved by metastatic malignancy. Postoperative cobalt 60 teletherapy was employed.

CASE III. C2071. M.M., a 46 year old female, stated that she had been aware of a mass in the upper outer quadrant of her left breast for 15 years. This was observed by her physician at regular intervals and was presumed to represent a benign cystic mass. Ten days prior to our examination, she noted that the entire outer aspect of the left breast became markedly prominent, tender and red. Physically, the left breast was much larger than the right. A poorly defined mass occupied most of the upper outer quadrant. A roentgenogram (Fig. 3*A*) showed slight generalized prominence of the skin and subcutaneous tissue. Numerous finger-like projections of infiltrating tissue following the run-offs of Cooper's ligaments were present and appeared to pervade the entire left breast. The changes were especially striking when compared with the opposite and normal breast (Fig. 3*B*).

A needle biopsy and skin biopsy were reported as inflammatory carcinoma. Therapy consisted of a simple mastectomy with postoperative cobalt 60 irradiation. This patient died 9 months following examination.

ROENTGEN FINDINGS

The most characteristic roentgen appearance is an over-all increased tissue density of the involved breast in contrast to the noninvolved breast. This increased density may be homogeneous (Fig. 1*A*) or consist of finger-like projections running perpendicular to the skin surface (Fig. 3*A*). The latter represent multi-focal areas of cancer which involve the lymphatics following the suspensory ligaments of Cooper.

Every case in our series had some perceptible increase in the thickness of the skin and immediately adjacent subcutaneous tissue. This finding was invariably extensive, with practically the entire breast surface being involved. In some instances there was clinical peau d'orange of one-half of the breast, yet mammography revealed thickening of the entire subcutaneous area.

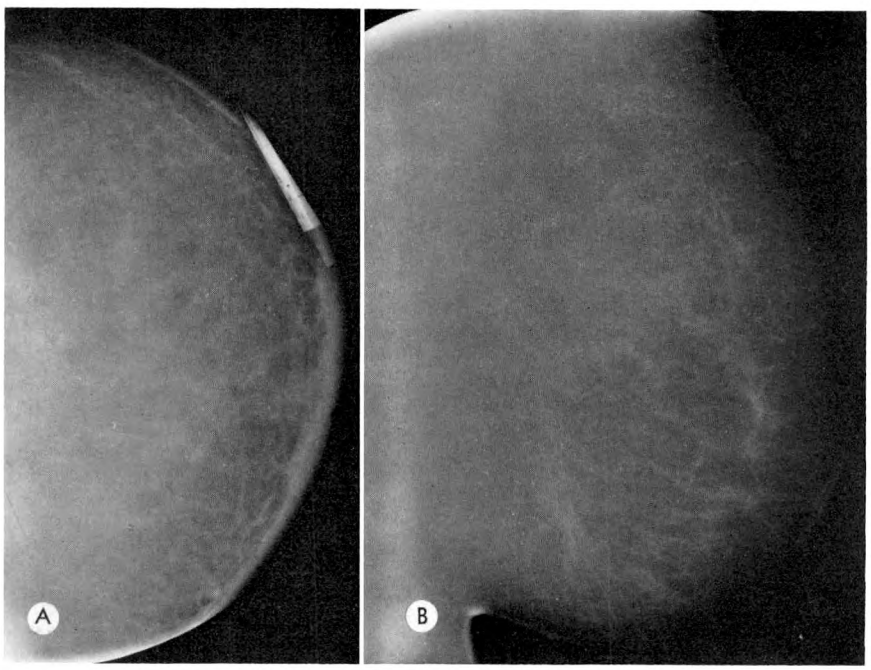


FIG. 3. Case III. (*A*) The left breast. Marked subcutaneous thickening, questionable visible prominence of lymphatic channels beneath the skin, and linear digitations of increased tissue prominence in the mid and lower thirds strongly suggest inflammatory carcinoma. (*B*) The normal right breast.

This is in contrast to the local or segmental prominence of the skin or subcutaneous area which one may find adjacent to an inflammatory process or to some scirrhous carcinomas.

A third and important feature is the roentgen identification of the actual prominent subcutaneous lymphatics. This reveals itself as a very fine streaking running perpendicular to the skin surface. The identification of this change calls for carefully and correctly exposed mammograms. In reference to this past finding, however, it should be noted that the differentiation of the type of lymphatic channel involvement is best evaluated by microscopy since it is possible to identify prominent lymphatic channels in an inflammatory lymphangitis as well as in inflammatory carcinoma or in the associated inflammatory reaction adjacent to a scirrhous carcinoma.

Recently, however, we have been following this lymphatic response by repeated mammography at weekly intervals. Figure 4, *A* and *B* reveals the change following antibiotics in a 70 year old woman suspected at first of having an inflammatory carcinoma. Mammography dramatically revealed the disappearance of the prominent lymphatic channels (Fig. 4*B*) in contrast to Figure 4*A*, which indicated that the process was merely of an inflammatory nature and not an inflammatory carcinoma.

DIFFERENTIAL DIAGNOSIS

1. *True Inflammation.* The skin over an abscess is usually smooth, shiny and tender, in contrast to inflammatory carcinoma where the skin is nontender, pitted, edematous and of the orange peel consistency. Inflammation usually has accompanying leukocytosis and fever, whereas most inflammatory carcinomas are not associated with fever or leukocytosis. An acute inflammatory process, either a beginning abscess formation or erysipelas, will generally respond rapidly to antibiotic therapy; and although one would presume that this feature in itself would help in making a differential diagnosis, the frequency with which inflammatory carcinoma is regarded as merely of nonspecific inflammatory etiology indicates the complexity of the problem.

The parenchymal reaction of very early and acute inflammation may frequently not have any roentgenographically apparent soft tissue opacification. However, as the process becomes more contained and organized, one can recognize a faint dominant soft tissue mass with irregular margins. Further organization is generally associated with increase in the degree of soft tissue density and clear definition of the marginal outline. Another inflammatory reaction that one must exclude is in those cases having redness and edema of the skin which merely represent a localized cutaneous inflammatory reaction at the site of skin attachment to a superficially located tumor, whether the tumor be benign or malignant. A rather frequently encountered

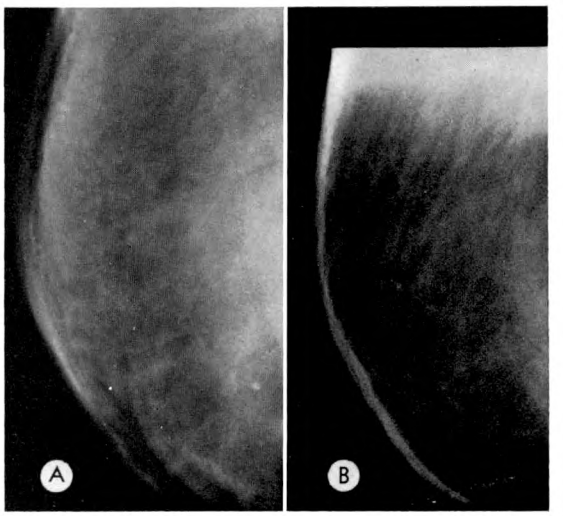


Fig. 4. (*A*) A 70 year old female with the clinical picture of inflammatory carcinoma. Mammogram reveals slight subcutaneous thickening, strikingly prominent lymphatic channels, and no definite mass effect. An inflammatory carcinoma was suspected. (*B*) One week after conservative therapy. The striking response with complete disappearance of the prominent lymphatic channels indicates the process to be that of an inflammatory lymphangitis.

entity that we have experienced is the process of perifocal inflammatory reaction around rather large and discrete cysts. Frequently, there is a history of some previous traumatic incident to account for the acute findings, although on occasion no apparent local traumatic incident occurred. Clinically, one is generally presented with a rather extensive and dominant mass without the usual clinical finding of a soft, sharply circumscribed cystic-feeling process, so that the clinical impression is one of questionable malignancy. Roentgenographically, one is able to identify the underlying cystic mass although its marginal outline may be obscured to some extent by the perifocal inflammatory reaction. The roentgen appearance is frequently the same in both breasts (Fig. 5, *A* and *B*). The dramatic clinical response to rest and antibiotics within 1–2 weeks confirms the benign nature.

2. *Plasma Cell Mastitis and Secretory Disease (Mammary Duct Ectasia).* Secretory disease is proliferation and uniform hyperplasia of all components of the duct wall and degeneration of the secretory cells which are cast off into the lumen. This is frequently identified on mammograms by the characteristic finding of prominent, irregular and beaded duct structures. Not infrequently there is evidence of linear calcification within the duct structures in both breasts.[3]

Plasma cell mastitis is a complication of secretory disease. Though not infrequently asymptomatic, there may be instances when the inflammatory elements are so prominent as to suggest an abscess. The process is painful, a mass is generally palpa-

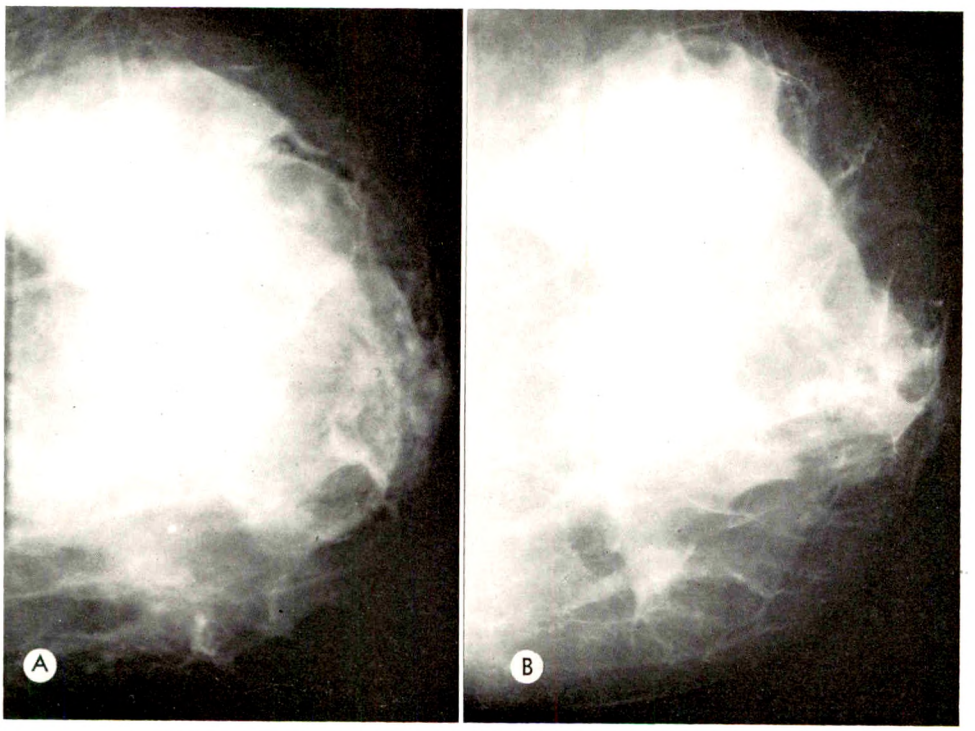


Fig. 5. (*A*) A 38 year old female with a sudden onset of a very tender large mass occupying the entire outer half of the right breast. There was a vague history of recent trauma. Mammogram reveals numerous large cysts scattered throughout the breast without thickening of the skin or any appreciable lymphatic response. (*B*) The opposite and "normal" breast also reveals a similar appearance and indicates bilateral extensive cystic mazoplasia to be present. The clinical problem in the right breast subsided in 5 days. Surgery was performed because of the persistence of a clinical mass and revealed numerous cysts.

ble and there is moderate skin redness. Roentgenographically, the mass has a uniform ground-glass appearance and a fuzzy marginal outline in contrast to the spiculated margins of scirrhous carcinoma.[3] There is generally bilateral evidence of secretory disease which is apparent roentgenographically. Although there may be nipple retraction due to the chronicity of this process, one does not find evidence of extensive subcutaneous tissue thickening such as is found in inflammatory carcinoma. The diagnosis of plasma cell mastitis may be suspected from the history and physical findings and is confirmed by the roentgen appearance. Examination of the nipple discharge frequently reveals fat-containing histiocytes which also aid in establishing a diagnosis.

3. *Chronic Granulomatous Inflammation Such As Tuberculosis.* This generally grows very slowly and the clinical course is not suggestive of acute carcinoma. Of 2 patients studied with tuberculosis, one revealed a large, very sharply circumscribed and marginated deep-seated soft tissue mass that could not be differentiated roentgenographically from a giant fibroadenoma, a lymphosarcoma or a chronic organized abscess; the other had a breast mass associated with evidence of underlying and associated pleural reaction.

4. *Radiation Dermatitis and Chemical Irritants.* Both of these cause marked skin reactions that should be adequately differentiated from malignancy with a proper history.

DISCUSSION

In reviewing our experience in inflammatory carcinoma, it was interesting to note that except in those instances where a discrete mass could be identified, the early attitude and reaction was to regard the changes as those of a nonspecific inflammatory lesion. However, after correlating our material, the advantage of using mammography to differentiate more adequately between true inflammatory problems or plasma cell mastitis and the entity of an inflammatory carcinoma became evident.

The review of this subject especially emphasizes a contention about which we feel strongly; namely, that mammography is best employed when evaluated in the light of a detailed history and physical examination. One must have these as a background so that a knowledge of the specific pathologic processes may be correctly correlated with the information that mammography can give. If the above grouping of necessary background factors is present, only then can the radiologist function as a worthwhile consultant in a very difficult problem.

SUMMARY

The roentgen criteria of inflammatory carcinoma have been discussed. Mammography permits one to identify the over-all increased soft tissue density of almost the entire involved breast or the finger-like projections of increased tissue infiltration. A second roentgen finding is an increase in the thickness of the skin and immediate subcutaneous tissue. The third finding is the presence of prominent and visible lymphatics in the subcutaneous region. All of these are especially evident when compared with the appearance of the opposite and normal breast.

Our experience has been too limited to evaluate the role of mammography as having any appreciable effect on the mortality rate of this most virulent cancer, since there has been invariable involvement of the axillary lymph nodes by the time the patient is examined, even though the history might only be of 10 days' duration. In spite of this, it does give one the satisfaction of helping in a very trying and discouraging clinical problem.

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THE DIAGNOSTIC IMPORTANCE OF CALCAREOUS PATTERNS IN ROENTGENOGRAPHY OF BREAST CANCER*

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LEBORGNE[8] in 1951 pointed out the special diagnostic importance of calcium deposits in the diagnosis of cancer by mammography. This was confirmed subsequently by other investigators.[2,4,9,10] Shepard, Crile and Strittmatter[12] recently reported an incidence of more than 75 per cent of these calcifications on roentgenograms of paraffin sections of all types of breast cancer. The surprising pathognomonic roentgenologic implications of these deposits have become evident to many radiologists during the past 12 years even though to the pathologist this phenomenon has no special diagnostic import.[1,2,4,10]

Not always are the calcium deposits confined to the tumor; they may be scattered and dispersed. When they are dispersed, the malignancy is more apt to be ductal. When calcifications are seen inside a nodule, the cancer is apt to be scirrhous. When both scirrhous and duct cancer are present simultaneously, the calcium deposits are usually seen in and beyond the confines of the visible tumor.

Forms of calcification other than the granular, punctate variety characteristic of cancer must be recognized in the breast. Fatty degeneration very often precedes calcium deposits. The occurrence of fatty degeneration leads to the formation of calcium soaps, proteinates, phosphates and carbonates. Therefore, aside from malignancy, any condition accompanied by fatty degeneration, such as secretory disease, traumatic fat necrosis, etc., will also show calcium deposits. In secretory disease, calcium deposits have their own curious appearance. The deposits are tubular in the walls of the ducts and appear as parallel streaks of calcification on the roentgenograms. The ducts and saccules may become plainly outlined.[3]

In inflammatory conditions of the breast, coarse types of calcium particles may also deposit in necrotic or fibrous tissue. Calcium deposits also occur in fibroadenoma for the same reasons. The flake or plaque-like character of these deposits makes recognition easy. Adenosis often reveals small globular or spherical deposits. Calcific arteriosclerotic vessels and phleboliths are not hard to identify.[5,6,7,11]

The most difficult conditions to be differentiated from malignant calcifications are those associated with intraductal epithelial hyperplasia. These deposits resemble those of duct carcinoma so that differentiation may sometimes be impossible. Since this condition may be precancerous, the advisability of diagnostic resection is seldom in question.

The following case reports are examples illustrating the importance of crystalline punctate calcium deposits in the diagnosis of breast cancer.

REPORT OF CASES

CASE 1. A 27 year old female was aware of a mass in her right breast for 5 weeks. She believed that the mass had decreased in size. A small mass in her right breast noticed one year before disappeared spontaneously.

Clinical examination revealed a freely movable and nontender mass, 6×6 cm. There was also a small nodule palpable in the left breast. No suspicion of malignancy was entertained.

Mammograms revealed a discrete lobulated mass with several areas of crystalline-like calcific deposits within it in the upper outer aspect of the right breast. Biopsy was advised

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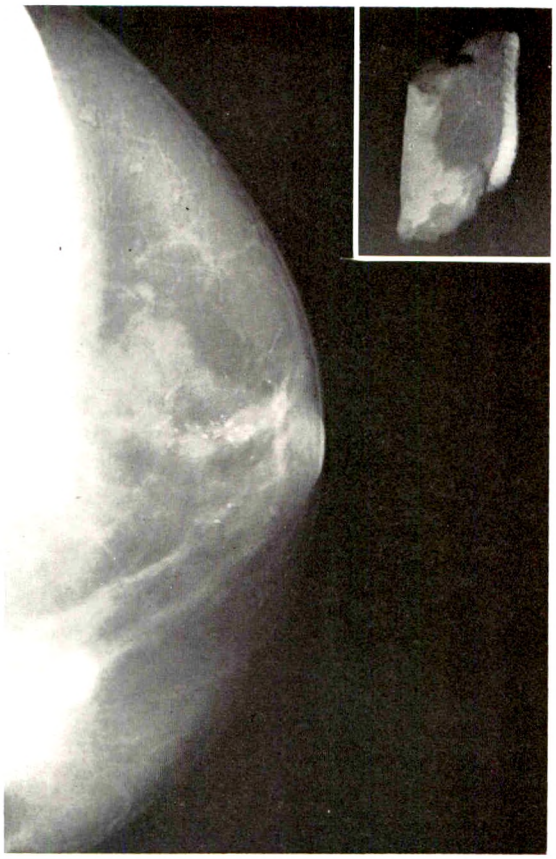


FIG. 1. Case I. Calcific deposits in a case of cancer of the right breast which was clinically diagnosed as a benign lesion. A portion of the resected specimen containing two deposits is illustrated on the insert of the upper right corner.

because malignancy was suspected. The lesion in the left breast was believed to represent fibroadenosis.

The right breast lesion was resected and carcinoma was diagnosed by the pathologist (Fig. 1).

Comment. This case illustrates how a malignant lesion can clinically mimic a benign process. In spite of the age of the patient and the clinical findings, the presence of calcium deposits led the roentgenologist to suspect the malignant process.

CASE II. A 41 year old female was admitted to the hospital for removal of a cyst in the upper outer quadrant of the right breast. She already had had bilateral operations for cysts.

The last of five serial roentgenographic studies made at 6-month intervals led to the recognition of a few granular calcific deposits which raised the suspicion of malignancy. In retrospect, these calcifications should have been recognized on roentgenograms made 18 months earlier, but were overlooked because the exposure was not of optimum density. At operation, cysts in the upper outer quadrant as well as a small duct carcinoma were found (Fig. 2).

Comment. This was a case of clinically

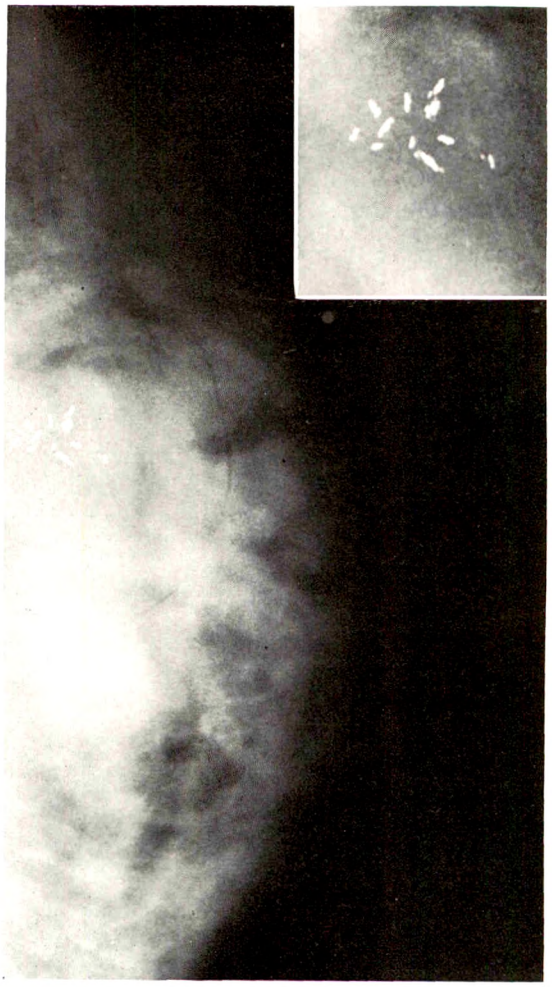


FIG. 2. Case II. A few calcific spicules were sufficient to make the roentgenologist suspicious of malignancy.* They had been overlooked on underexposed roentgenograms for 18 months. Only cysts were suspected by the surgeon, but the pathologist found in addition a duct carcinoma.

*The calcific deposits in Figures 2 to 10 are partially retouched; their size and shape have not been altered, but the density contrast has been increased. The inserts are reproductions of the calcium deposits magnified two times.

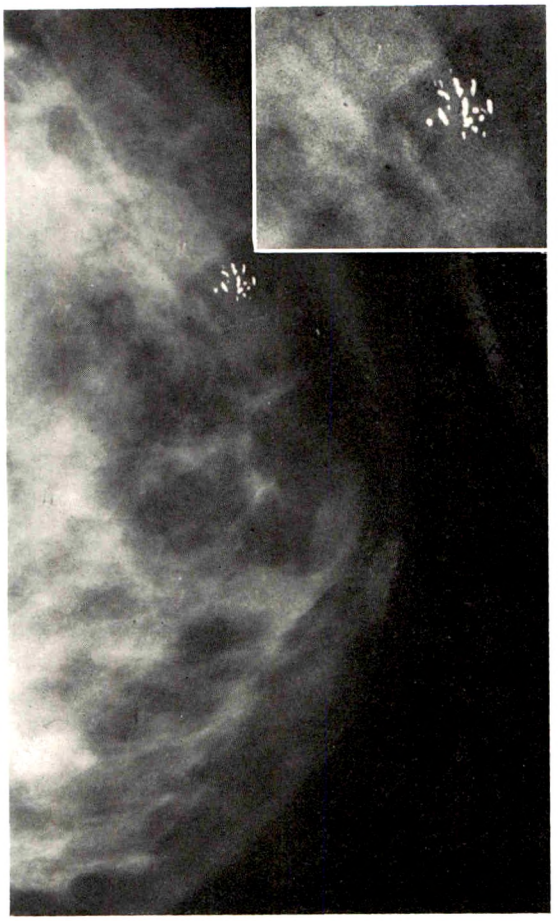


Fig. 3. Case III. Calcific deposits in duct carcinoma which confirmed clinical impression.

unsuspected carcinoma in a patient admitted for removal of a cyst. Illustrated also is the necessity for a search on properly exposed roentgenograms for small punctate calcifications. Over-exposed roentgenograms viewed with bright transillumination and a magnifying glass are helpful aids which we now use routinely.

Case III. A 59 year old female noticed a lump in the left breast for about a year. It was asymptomatic and no change was noticed in size during this period. A mass of 2×3 cm. in the left breast was found which was firm, slightly lobulated, nontender, and fixed to the skin but not to the underlying fascia. A single lymph node was present in the left axilla.

Mammograms showed a mass containing many small granular flecks of calcium. This finding strongly supported the clinical diagnosis of malignancy and surgical interference resulted. The pathologic diagnosis was infiltrating duct carcinoma of the left breast with metastasis to the axillary lymph nodes (Fig. 3).

Comment. The presence of calcium deposits confirmed the clinical impression of malignancy in this case and helped to avoid surgical delay.

Case IV. A 49 year old woman discovered a tender nodule in the right breast just below the nipple 3 days prior to admission. The nodule measured 1 cm. in diameter and was considered benign clinically. Mammograms revealed a tiny clump of calcific particles and biopsy was advised because malignancy was suspected. The pathologic diagnosis was partly scirrhous, partly large cell duct carcinoma with metastasis to 2 of 16 axillary lymph nodes (Fig. 4).

Comment. A small tender nodule in the breast is often regarded by physicians as

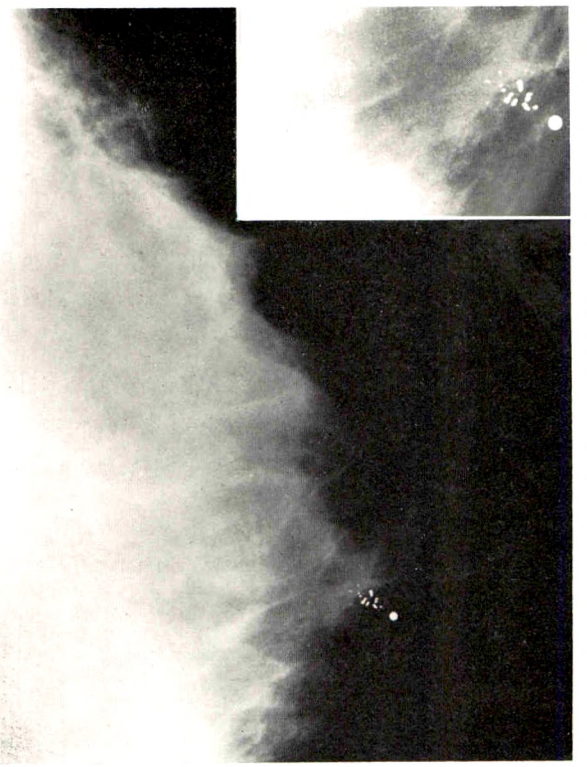


Fig. 4. Case IV. A few calcific spicules led the roentgenologist to suspect malignancy which was contrary to the clinical findings. Duct carcinoma was found.

insignificant. With mammography, identification of tiny clumps of calcium led to the suspicion of malignancy.

CASE V. A 53 year old woman joined our breast survey project for periodic roentgen examination of asymptomatic patients in January, 1956. Her breasts were large and pendulous. The initial examination revealed several small fibroadenomata in the upper outer portion and one moderate-sized cyst or fibroadenoma in the upper inner quadrant of the right breast. The patient was re-examined routinely every 6 months.

The clinical and roentgenologic findings remained essentially unchanged until February, 1960. Roentgenograms then showed a density with irregular margins associated with calcium deposits. Biopsy was advised, but refused.

Subsequent routine examination 6 months later showed a slight increase in calcification. Biopsy was again recommended and the location for biopsy was planned from the roentgenographic findings. The patient finally consented to surgery 2 months later, but only a fibroadenoma was removed from the inner aspect of the right breast. The suspicious area containing the calcifications had not been resected.

Re-examination in February, 1961 revealed a slight increase in the amount of calcifications. Biopsy of this area was again recommended, but the patient refused surgery until May of 1961. Operation at that time yielded a resected specimen from which a pathologic diagnosis of "resected fatty breast tissue with adenosis" was made.

The patient was not re-examined until November, 1961, at which time more calcium spicules were visible. Biopsy was again recommended and this was done in December, 1961. From the frozen section an inconclusive diagnosis was made but microscopic studies later revealed duct carcinoma with extension to a small adjacent fibroadenoma. Radical mastectomy was then done. No residual carcinoma was found. Several small fibroadenomata were noted scattered throughout the breast. There was no metastasis to any lymph nodes (Fig. 5).

Comment. This case illustrates how slowly a malignant lesion may grow. The reliability of roentgen diagnosis of a small, nonpalpable early carcinoma was again based on the presence of stippled calcifications. Postoperative roentgen studies are necessary if the pathologist is unable to confirm the roentgenologic opinion since the lesion may not have been resected.

CASE VI. A 76 year old female joined our asymptomatic breast survey group in June, 1956. Initial roentgen examination of the breasts showed minimal secretory disease.

The patient was re-examined at 6 month intervals. After the second examination in November, 1956, a few tiny calcium deposits were noted in the right breast which suggested the presence of intraductal epithelial hyperplasia. Each succeeding examination showed no appreciable change. However, when the examination of December, 1961 was compared with all the previous studies, a definite increase in the number of calcium deposits became obvious and a biopsy was then recommended. At operation, a small carcinoma was found with no evidence of axillary metastasis (Fig. 6).

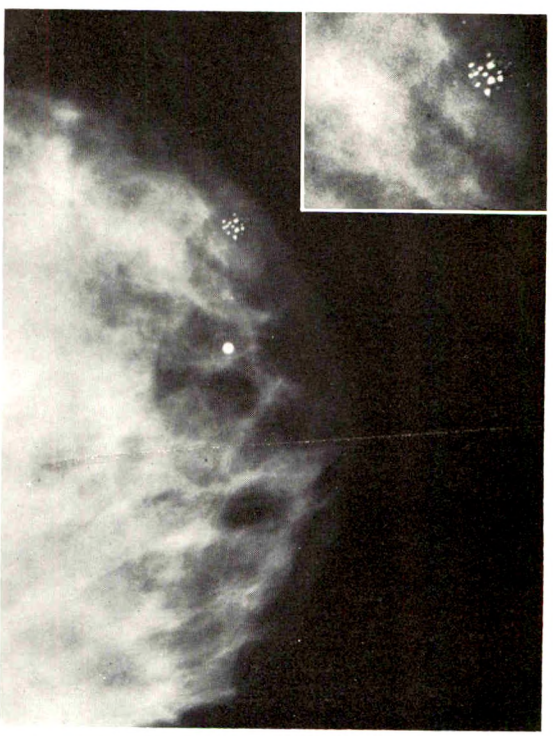


FIG. 5. Case v. Punctate calcifications in a duct carcinoma. Only after 3 biopsies was the lesion finally removed. The true nature of the process was not evident from gross examination of the resected specimen, but only from its microscopic appearance.

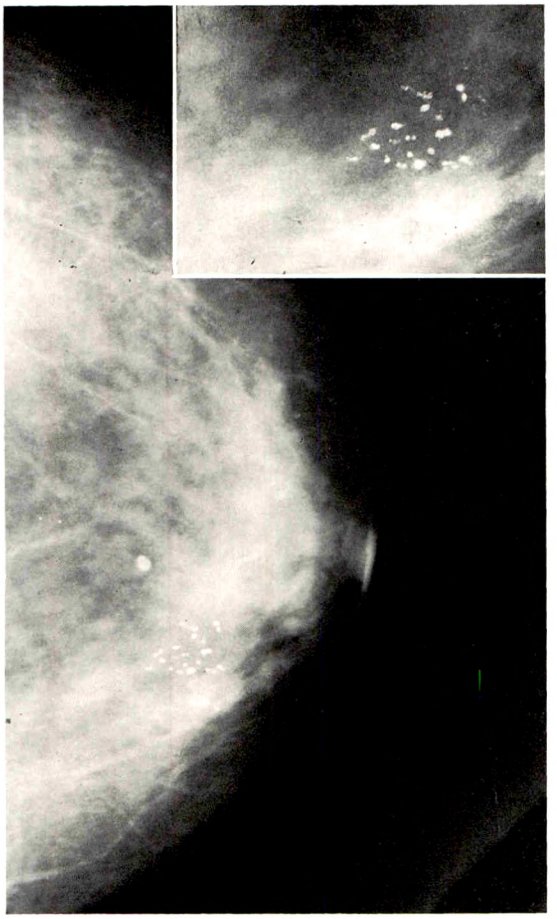


Fig. 6. Case vi. Minute granular calcifications in a nonpalpable duct carcinoma observed for $5\frac{1}{2}$ years before operation.

Comment. This case demonstrates the difficulties of differentiating calcium deposits due to intraductal epithelial hyperplasia and malignancy. It also stresses the importance of appreciating increases in these deposits with re-examinations. Revealing to us was the slow growth of this cancer which was not associated with axillary metastasis even after $5\frac{1}{2}$ years of observations.

Case vii. A 42 year old patient discovered a mass in her right breast of 3 weeks' duration. A movable, hard, slightly tender mass was palpable in the upper outer quadrant. The clinical impression was a benign cyst. Aspiration of the mass was attempted by the clinician, but no fluid was obtained. Mammograms showed multiple coarse calcific deposits scattered throughout both breasts typical of calcification in adenosis. In addition, however, a tiny clump of fine calcium deposits was identified and these findings raised the suspicion of carcinoma. A small infiltrating duct carcinoma with multiple cysts was found (Fig. 7).

Comment. Here again, the clinician thought that a cyst was present. The demonstration of tiny calcium deposits, however, led to a roentgenologic diagnosis of carcinoma. The coarse globular calcium deposits seen in adenosis are not to be confused with the fine granular type of calcium

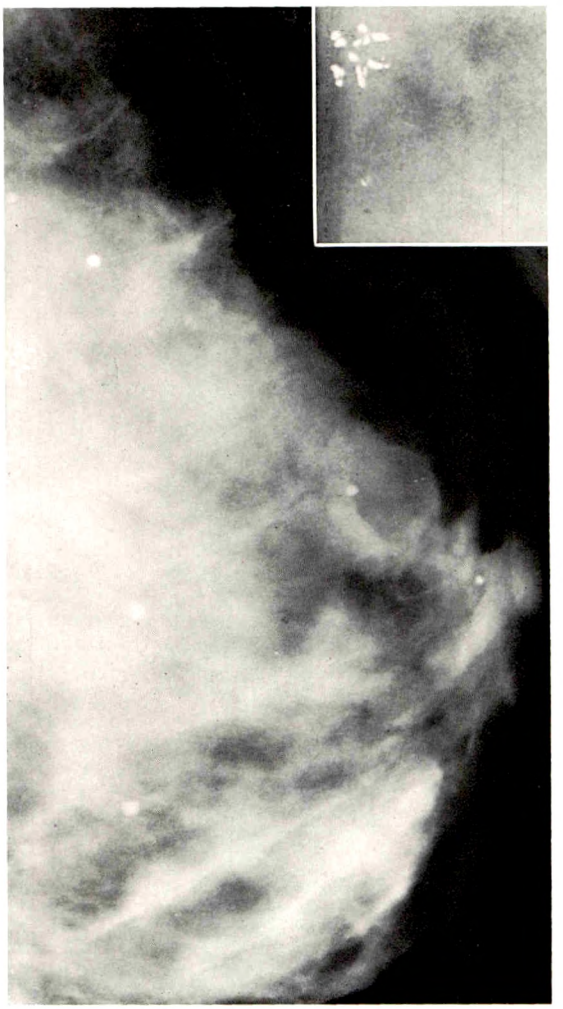


Fig. 7. Case vii. Minute calcific spicules indicate a duct carcinoma. The isolated beads of calcification scattered throughout the breast often are seen in association with adenosis.

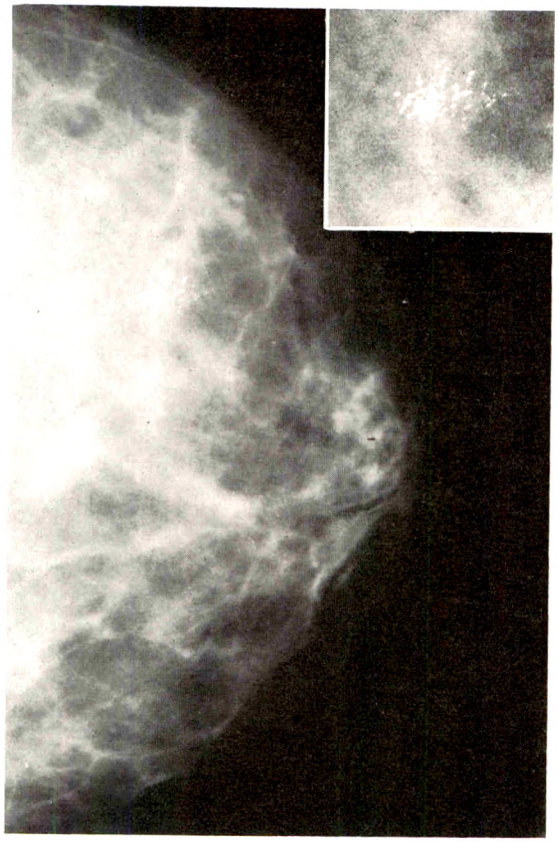


FIG. 8. Case VIII. A cluster of calcium spicules indicated a malignant process in the right breast. The patient consulted her physician because of pain in the left breast which was found to be normal.

deposits seen in carcinoma; both types were present in this breast.

CASE VIII. A 47 year old female presented herself with a complaint of intermittent pain in the upper outer quadrant of the left breast following a hysterectomy done one year previously. Clinical examination revealed nodularities bilaterally with a slightly tender area in the upper outer quadrant of the left breast. Roentgen examination showed calcification associated with a small mass in the asymptomatic right breast. This was reported as highly suspicious of duct carcinoma. Biopsy of this area was advised. A quadrant dissection of the area revealed a tiny mass which on frozen section was found to be malignant (Fig. 8).

Comment. This patient complained of pain in the left breast and roentgen studies revealed carcinoma in the asymptomatic right breast. The reliability of the roentgenologic diagnosis based on these granular calcium deposits is again exemplified.

CASE IX. A 52 year old patient was referred by her family physician because of occasional pain in the left breast. The breasts were lumpy and a small movable nodule, 1 cm. in diameter, was found in the upper outer quadrant. Mammograms showed fine stippled calcific particles in this area suggestive of carcinoma and a biopsy was performed. The frozen section revealed a benign lesion, but the final histologic studies revealed duct carcinoma. Adenosis with calcification also was present. Subsequently, radical surgery was performed. There was no lymph node metastasis (Fig. 9).

Comment. As in the previous cases, carcinoma was diagnosed by roentgen exami-



FIG. 9. Case IX. A few stippled calcium deposits suggested the presence of carcinoma in an area of adenosis. The larger circular calcium deposits seen in adenosis are not easily confused with the granular or spiculated deposits associated with malignancy.

nation purely on the identification of the calcium deposits, and the roentgenologic diagnosis was more accurate than the frozen section studies. The larger globular deposits of adenosis do not resemble the smaller granular deposits of cancer.

Case x. A 54 year old female had a history of scabbing of the left nipple for a period of 6 months. No mass was palpable. Mammograms showed a small clump of calcium particles with infiltration beneath the left nipple suggestive of Paget's disease. Spiculed calcific particles extending posteriorly from the nipple were also seen, suggesting ductal extension. Paget's disease of the nipple with duct carcinoma of the major ducts of the breast was found by the histologist (Fig. 10).

Comment. This case, like the others, showed the typical punctate calcium particles of mammary cancer. The concept that Paget's disease of the breast usually is associated with duct carcinoma is also supported.

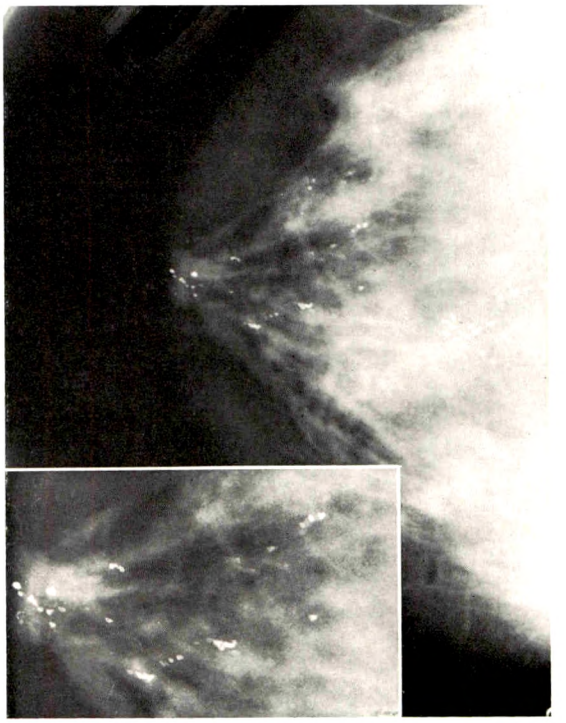


Fig. 10. Case x. Widely scattered minute spicules of calcification in Paget's disease and duct carcinoma.

DISCUSSION

The calcium deposits of mammary cancer were first described by Leborgne,[8] and he states in his book,[9] "Calcifications are generally tiny, dot-like or somewhat elongated, innumerable, and irregularly grouped very close together in an area of the breast, resembling a powdering of fine grains of salt." We have found this to be one of the most important signs in the diagnosis of mammary cancer, especially of duct carcinoma.

Among the last 300 cases of mammary cancer, a roentgenologic diagnosis of malignancy was made in 91 based on the presence of calcium deposits; 18 of these were operated on although no palpable tumor was present.

An illustration in this connection is the following: a 43 year old patient presented with a lump in her right breast which was diagnosed as a benign process by the clinician. The presence of a few granular calcareous deposits led the roentgenologist to suspect carcinoma (Fig. 11 *A*) and so the surgeon consented to operate. The pathologist reported cystic disease with no evidence of malignancy. From similar previous experience, it was realized that the tissue containing the lesion suspected by the roentgenologist may not have been excised, so it was suggested that this patient be re-examined. Mammograms seven months later (Fig. 11 *B*) revealed the presence of more dense granular deposits, but because of the absence of a palpable mass, the surgeon refused to operate, especially since the pathologist after the first biopsy reported a benign process. Thirteen months later, the patient was re-examined and this time, more granular calcareous deposits were found scattered throughout the breast (Fig. 11 *C*); surgery was again refused because of the absence of a palpable mass. A re-examination about 15 months later at the request of the roentgenologist revealed the presence of increased deposits and this time (Fig. 11 *D*), in spite of the absence of a palpable tumor, the surgeon was prevailed upon to

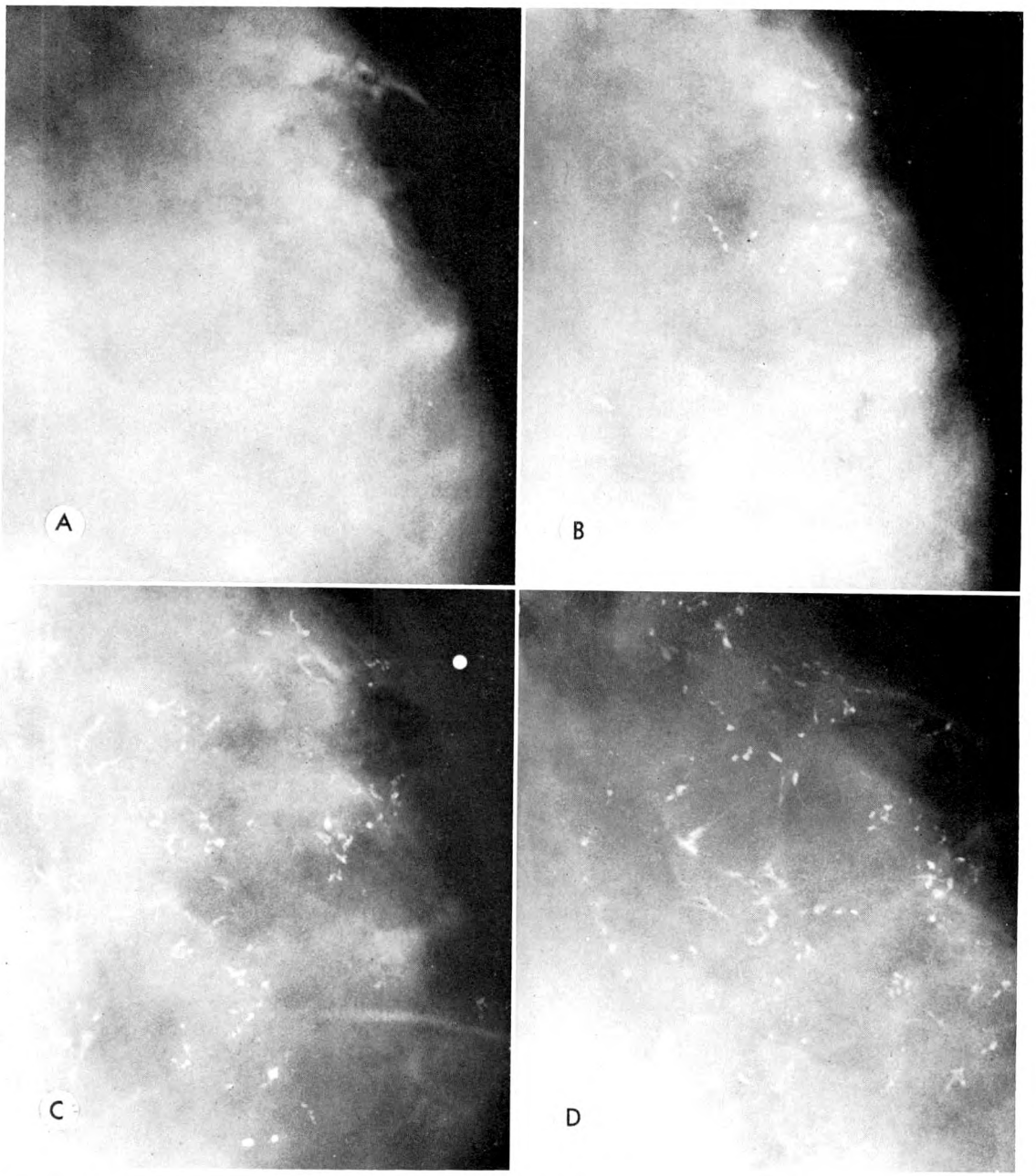


FIG. 11. (*A*) *August 5, 1959:* Duct carcinoma was suspected by the roentgenologist because of the presence of a few granular calcareous deposits. The clinician regarded a palpable lump as benign and the pathologist reported cystic disease in the resected tissue. (*B*) *March 23, 1960:* Examination 7 months later revealed more calcareous deposits, but the surgeon refused to operate because of the absence of a palpable tumor. (*C*) *April 21, 1961:* Thirteen months later, examination again revealed more scattered calcareous deposits, but no mass was palpable and surgery was not performed. (*D*) *June 1, 1962*: Re-examination some 15 months later revealed extensive dispersal of calcium deposits. At this time, surgery was carried out in spite of the absence of a palpable mass. A widely disseminated duct cancer was found, fortunately with no evidence of metastasis to the axillary lymph nodes. (The reproductions in this case are unaltered and the calcific deposits are not retouched.)

operate. An extensive duct carcinoma was found, fortunately not yet associated with metastasis to any of the resected axillary lymph nodes.

In cases with multinodularity, the finding of granular calcium deposits whether localized to the area of symptoms, or elsewhere in the breast, or even in the opposite breast as occurred in Case VIII leads immediately to the proper diagnosis of malignancy. Many lesions which seem entirely innocuous harbor these calcium spicules. Most important is the finding of these deposits in the absence of a palpable tumor or other clinical signs of malignancy. Slowness on our part to appreciate the significance of this situation gave us an opportunity to study the growth rate of breast cancers from which we have gained the impression that many are slow-growing and chronic in nature.

Knowing the importance of these fine calcium deposits in the diagnosis of mammary cancer, the radiologist should be very careful to obtain well-exposed roentgenograms which are best examined with brilliant transillumination. Differentiation between malignant and benign calcifications can usually be made except in occasional cases of intraductal epithelial hyperplasia. Then serial studies will help since increase in the number of calcifications is more apt to occur in cases of cancer; however, diagnostic resection is advisable in either case. With further improvement in technique, these calcifications may be visualized in a greater number of instances, thus enabling an accurate early diagnosis often when the lesion is small and not yet palpable. Here lies the challenge for the immediate future.

SUMMARY

The importance of recognizing characteristic fine granular calcium deposits on roentgenograms in the diagnosis of mammary cancer is stressed. Ten cases are presented showing the reliability of the roentgenographic findings. Approximately 30 per cent of cancers can be detected by these calcium deposits, but with further improvement in technique, a higher percentage will be found, even when lesions are too small to be palpable.

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ROENTGENOGRAPHY OF THE MALE BREAST*

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ROENTGENOGRAPHIC examination of the male breast is an important aspect of the continual, intensive investigation of the radiologic morphology of the normal and diseased breast conducted in our Department over a period of 12 years. It is the purpose of this report to present the roentgen appearance of various lesions of the male breast as they have been found in our practice and also to stress some of the difficulties in the differential diagnosis of these lesions. It should be stressed again, as in previous reports from our Department (Gershon-Cohen, Berger *et al.*), that we do not regard mammography as a substitute for biopsy, especially in a part of the body that is so easily accessible surgically as the breast, and in this instance, an even more accessible part, the male breast. Through long experience we have also come to realize that there is no substitute, short of histologic examination of the tissue in question, for clinical judgment in handling any breast lesion. Regardless of the characteristics of any mass shown on roentgenograms, the history of the development of the lesion, its palpable characteristics, the family background and psychologic make-up of the patient also are important determining factors in deciding whether a mass in the breast should be removed for biopsy purposes.

While roentgen diagnosis of a mass in the breast affords a definite measure of certitude in evaluating its benign or malignant nature, we have seen round, smoothly marginated tumors which were diagnosed benign roentgenographically turn out to be highly malignant cancers on biopsy and, conversely, masses with all the roentgen criteria of infiltrating carcinoma eventually have been shown to be benign processes. However, our studies of over 1,300 women in our Breast Research Clinic and our evaluation of several thousand masses in privately referred women, together with our studies of lesions in the male breast, confirm the correctness of an attitude of confidence in the roentgenographic examination of the breast.

PROCEDURE AND TECHNIQUE

Our roentgenographic studies of both the male and female breast are done with the patient in the erect and recumbent positions. A flat-sided cone is pressed against the chest wall to provide collimation of the roentgen-ray beam. For optimum contrast we use non-screen films, 30 kv. and 100–250 mas. with a focal spot of 0.8 mm. at a film-target distance of 35 cm. Variation in the mas. factor will depend on the size and solidity of the breast: the young virginal breast will require doubling or tripling of the mas. factor, whereas an atrophic breast with much fatty infiltration requires reduction in the kilovoltage and mas. factors. A particularly useful procedure has been to affix a small lead shot over any painful area or palpable lesion by means of transparent tape. Further spot compression roentgenograms may be taken in whatever projection necessary to bring the suspicious area closest to the film.

Because of the pyramidal contours, uniformly good contrast of all breast structures is difficult to obtain on one roentgenogram. Thus the superficial portions of the breast are overexposed if good contrast of the deep structures has been demonstrated; conversely, deeper portions near the chest wall will be underexposed when the anterior segment of the breast shows good contrast. To overcome this, two non-screen

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films may be exposed simultaneously, interposing a thin foil of aluminum, 0.5 mm. in thickness. The upper film then shows good contrast of the thicker portions of the breast, and the film covered by the aluminum foil shows good contrast of the anterior portions of the breast. With one exposure totaling no more than 0.5 r to the skin, two clearly delineated roentgenograms of the breast have thus been successfully obtained. It is of the greatest importance to obtain good roentgenograms. Technically inadequate roentgenograms have been perhaps the greatest single obstacle to more widespread use of breast roentgenography.

In our clinic the patient is interviewed by a registered x-ray technician who fills out a clinical history sheet. After this, the history is checked by a Staff Radiologist or Resident Radiologist and the breasts are thoroughly examined with the findings noted on a specially designed diagram of the breast area. A small lead shot, as previously mentioned, is affixed to the skin overlying the palpable mass or masses and roentgenograms are made. In all cases careful correlation of the roentgenographic appearance with the clinical history and physical findings is essential. It is important to understand this since shadows on breast roentgenograms are subject to errors of interpretation quite similar to those errors which may be made in roentgenography of other portions of the body. Thus, a hazy, poorly circumscribed area of density in the lung may be due to pneumonitis, infarction or tumor; and similarly, such a shadow in the breast may be inflammatory, neoplastic, or adenotic. The clinical background, therefore, is just as important in interpreting a shadow in the breast as it is in viewing a similar shadow on a chest roentgenogram. Some shadows may be quite diagnostic in some cases, but others may be subject to interpretation according to the clinical background and palpable findings.

RESULTS AND DISCUSSION

The following is a tabulation of conditions found in our male cases:

I. Gynecomastia	87
Adolescent Gynecomastia	11
II. Carcinoma	8
III. Inflammatory Process	7
IV. Papilloma	2
V. Benign Tumor	4
VI. Normal	6
Total	125

It is not intended in this report to discuss the accuracy of roentgen diagnosis of these lesions, but rather to describe and illustrate their roentgen appearance for purposes of general information and as an aid to those who may wish to develop mammography as a part of their working armamentarium. Approximately half of our cases have been operated upon so that tissue diagnosis is available in many instances. Illustrated cases in this report consist only of those in which the diagnosis has been confirmed by histologic examination with the exception of the case in Figure 3*B*, the adolescent cases, and 3 of the 4 adult gynecomastia cases which have been reasonably substantiated clinically and by follow-up. These have been selected for purposes of illustration because of difficulties in photographic reproduction of other histologically proved cases.

NORMAL MALE BREAST

In normal fatty male breasts the roentgen picture consists merely of rather homogeneous radiolucent tissue with no more than a few strand-like fibers located beneath the nipple corresponding to a few residual ducts and fibrous tissue. Sometimes the strands show a slight amount of confluence (Fig. 1).

GYNECOMASTIA

In our studies we have found that the roentgen picture described by the French authors[1,2] corresponds closely with that seen in many of our 98 cases. We have seen two main types of configurations, namely:

1. Dendritic: (same term used by French authors) consisting of a central density with prominent projections into surrounding fatty tissue. Variations in the number and size of the dendrites are quite common and

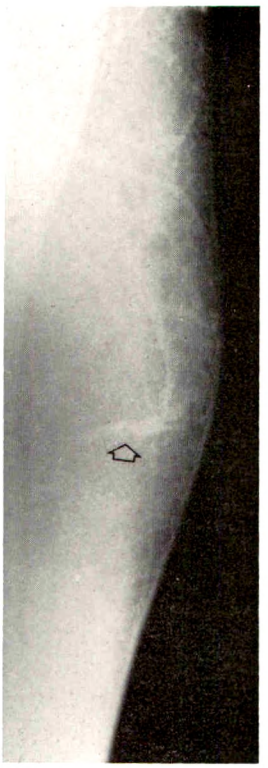


Fig. 1. Typical normal male breast showing mostly fat with a strand-like density (arrow) representing a few residual ducts and fibrous tissue.

include those cases with only a few, fairly prominent spicules as well as those that exhibit a mottled shadow consisting almost entirely of prominent and irregular dendrites (Fig. 2, *A*, *B* and *D*).

2. Non-dendritic: relatively well-circumscribed density with practically no discernible projections (Fig. 2*C*). (Nodular or triangular of the French authors.)

According to Amalric and Geller,[1] the dendritic type of configuration is seen in those cases of gynecomastia that show proliferation of ducts and the nodular (non-dendritic) type in those cases with proliferation of acini or lobules. We have not as yet been able to confirm this histologically. Of our 98 cases of gynecomastia, 40 were operated on. The roentgenographic diagnosis was proven incorrect in 2 cases: 1 case was thought to be a malignancy and the other a cyst; both were proven to be cases of gynecomastia.

Summarizing gynecomastia, it is quite interesting to note that in this condition we see a number of configurations resembling those seen in women, perhaps corresponding to the degree of development of the gynecomastic process and varying according to the component of the breast involved, *i.e.*, ducts, acini, or fibrous tissue as described by Amalric and co-workers[1–4]. This we hope to make the subject of a future report.

Adolescent Gynecomastia

For descriptive purposes we have grouped our 11 cases of adolescent gynecomastia separately because they present an interestingly uniform type of configuration corresponding to an essentially non-dendritic or only slightly dendritic type. Every case characteristically exhibited a relatively homogeneous density with a rather well-circumscribed margin with or without a few associated dendrites. It would seem of great value and interest to compare this with the experience of others when material becomes available in the literature. If this proves to be characteristic of the adolescent form of gynecomastia, it will perhaps make easier the recognition of other abnormal processes which might otherwise be confused with it roentgenographically (Fig. 2, *E* and *F*).

Inflammatory Processes

In our 7 cases of roentgenographically diagnosed inflammatory disease, we found most often a pattern of patchy density with spicule or dendrite formation sometimes with thickening of the overlying skin. As would be expected, this picture corresponds in every way to the configuration found in inflammatory lesions of the female breast and especially plasma cell mastitis with secretory disease. From the known histologic characteristics of inflammation, one would expect difficulty in differentiating its roentgen picture from that of carcinoma in many cases. This can be appreciated by comparing Figure 3*B* with Figure 6*D*. There may be a somewhat greater degree of localized density, however, in carcinoma

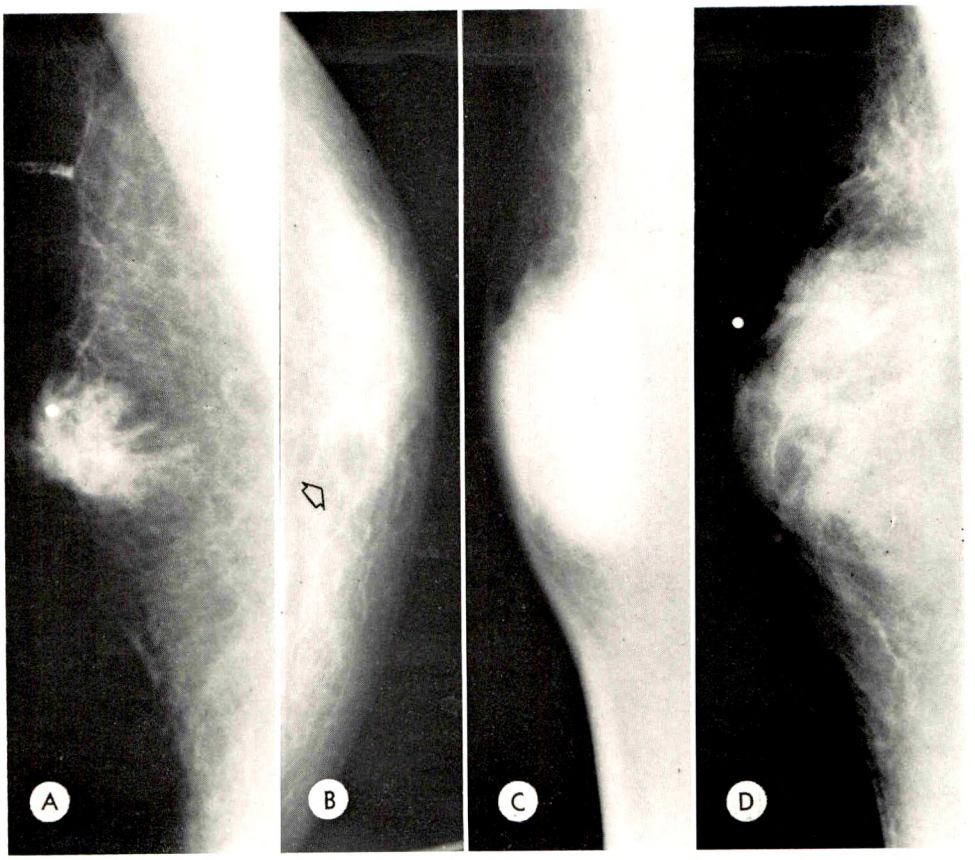


FIG. 2. (*A*) Dendritic gynecomastia. Note the prominent root-like projections extending into the surrounding fatty tissue, particularly posteriorly. This resembles the adenosis of females. This patient is still in good health more than 2 years later and has no clinical evidence of breast cancer. (*B*) A more confluent type of gynecomastia (anteroposterior projection). A few fairly prominent dendrites are visible at the medial aspect of the mass (arrow). This configuration is similar to that seen in mazoplasia fibrosa of the female breast.[7] (*C*) Non-dendritic gynecomastia. Almost no dendrites are seen. One or two very small and inconspicuous projections are visible at upper border of mass. This type of picture is noted in adolescent females. The operative specimen was composed of moderately firm, gray-white tissue, interspersed with small amounts of lobulated yellow fat. On section, numerous small, slightly elevated tan nodules were found. Microscopic diagnosis: gynecomastia. (*D*) Extensive, irregularly dendritic type exhibiting a mottled network and closely resembling the configuration of an adult female breast. The patient, a 25 year old male, originally complained of fullness and marked tenderness in the breast. On roentgen re-examination 10 months later, there was essentially no change, although the patient believed the breast was slightly smaller and non-tender.

as contrasted with a tendency for the infiltration in inflammatory processes to be somewhat scattered or diffuse. This is not entirely reliable, especially in cases with local abscess formation, and the necessity for careful clinical examination and history-taking becomes obvious. On the other hand, the roentgenographic characteristics have also been found similar on occasion to those of gynecomastia (Fig. 6*F*). The roentgen findings in the opposite breast are also quite helpful here since inflammation will usually be a unilateral process and gynecomastia a bilateral process (Fig. 3, *A* and *B*).

BENIGN TUMOR

In our cases of various benign tumors (mostly cysts), the outstanding feature was, of course, a smoothly marginated den-

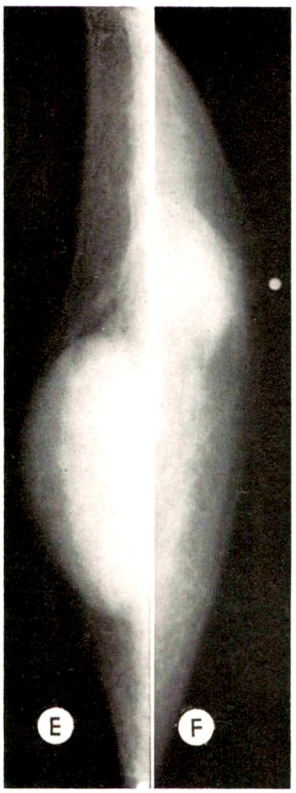


Fig. 2 (*E*) Adolescent gynecomastia. Most cases in our series exhibited the above configuration consisting of a well-circumscribed mass with rather sharply defined borders. Note the resemblance between this encapsulated appearance and the sebaceous cyst in Figure 4*B*. No diagnostic difficulties should be encountered in differentiation between these two possibilities because of the age of the patients and the clinical backgrounds. (*F*) A slightly less well-marginated adolescent gynecomastia representing another commonly seen variation of this condition (anteroposterior projection). Note the tendency to form a few small dendrites at the edges of the mass adjacent to the lead shot.

sity corresponding to the palpable nodule. With properly made roentgenograms these are obvious and usually quite easy to diagnose (Fig. 4, *A* and *B*).

PAPILLOMA

Our 2 cases of papilloma have been grouped separately because they presented much greater difficulty in roentgen diagnosis than the other benign masses in our series. One case (Fig. 5*A*) showed merely a slight amount of spiculated density with a few larger dendrites and the other (Fig. 5*B*) exhibited a questionable, somewhat rounded mass. Also in the latter case there was a suggestion of slight nipple retraction and thickening of the areolar skin which led to an erroneous impression of possible malignancy.

CARCINOMA

Of our 8 cases of carcinoma, 6 were believed to be suspicious of malignancy roentgenographically. The remaining 2 cases were felt to be benign but were subsequently proven at operation to be scirrhous carcinoma. In general, the roentgen picture is a variable one as in malignancy of

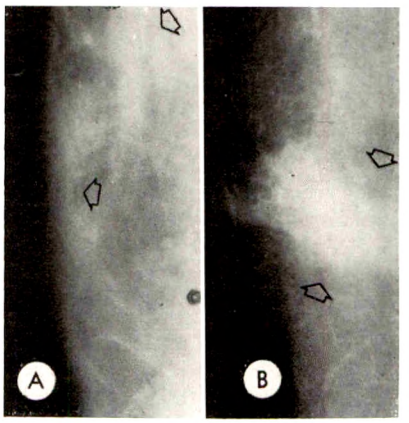


Fig. 3. (*A*) Inflammatory process. Note the thick skin (lower arrow) and spiculated infiltration (upper arrow) deeper in the breast. This patient presented a small painful lump of 1 week's duration and a slight elevation of temperature to 99°. Microscopic examination of the excised specimen revealed severely inflamed subcutaneous tissue with abscess formation. (*B*) A more localized type of inflammation extending deeply into the soft tissue of the breast. Note the extremely dense shadowing in the deeper portion of the lesion marked by arrows. This type is difficult to differentiate from carcinoma (see Fig. 6*D*). In this instance a nodule with tenderness was noted by the patient 2 months prior to roentgen examination. The nodule disappeared under medication by a private physician but the tenderness persisted. No operation was carried out but re-examination 26 months later revealed the patient to be completely asymptomatic. Roentgenograms showed marked improvement with practically complete resolution of the infiltration and only a few fibrous appearing strands remaining.

the female breast, but the most typical case exhibited a local, irregular, rather dense infiltration with spicules usually located eccentrically in relation to the nipple. At least 1 case had rather smooth margins, however, and another case showed lobulations. One case presented a patchy, stringy type of density rather than the condensed, opaque lesion usually expected in carcinoma. This is consistent with our experience with the female breast where, contrary to previous belief, carcinoma does not necessarily reveal itself as a very dense, localized, spiculated mass. Secondary signs such as thickening of the skin and retraction of the nipple are helpful but may also be seen in inflammatory disease (Fig. 6*A*).

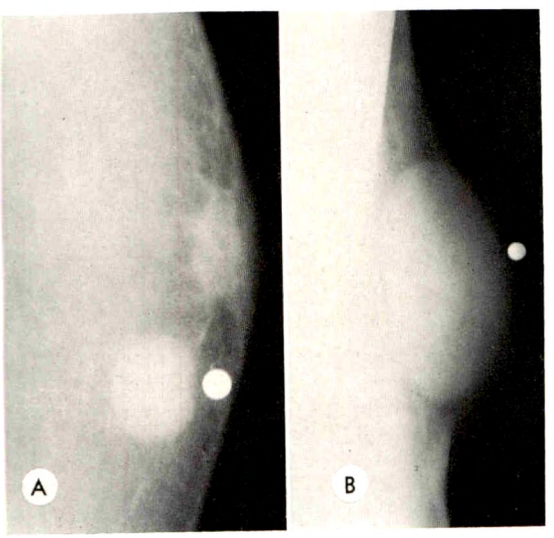


Fig. 4. (*A*) Sebaceous cyst (cephalo-caudad projection). A homogeneously dense and sharply marginated mass deep to the lead shot, easily diagnosed as a benign lesion. A sebaceous cyst, of course, is actually a skin lesion rather than a lesion of the breast itself. (*B*) Another sebaceous cyst. Again note the smooth borders of the tumor showing no sign of infiltration into the surrounding tissues. The great similarity between the appearance of this lesion and that of adolescent gynecomastia in Figure 2*E* is quite apparent. No difficulty in diagnosis should arise here because of the age of the patient and the usual clinical history. This patient complained of a lump growing steadily larger over a period of 1 month, increasing from the size of a pea to 3 cm. in diameter. Clinically, the mass was soft, elastic and movable. The opposite breast was normal. Operation revealed a 3×2 cm., translucent, thin-walled cyst filled with pale, foul sebum.

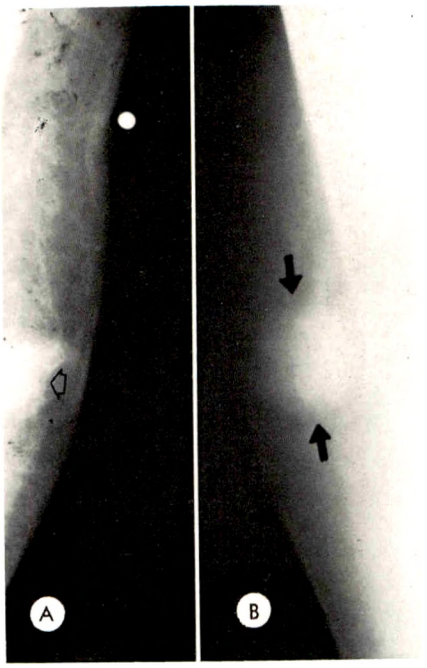


Fig. 5. (*A*) This is a case of papilloma. The abnormal density beneath the nipple has no particularly distinguishing characteristics except that on the original roentgenograms the area marked by the arrow appeared somewhat discrete and probably represented the area of actual tumor. This patient, a 68 year old male, complained of a dark brown discharge from the nipple for a rather indefinite period of 6 to 12 months with some questionable preceding chronic low-grade trauma to the breast as a result of his occupation. Microscopically, this was shown to be an intraductal papilloma. (*B*) A papilloma in a 78 year old man showing a somewhat rounded mass with faintly irregular borders (arrows). The patient experienced pain and discharge from the nipple for several years and presented with a firm, fixed, tender subareolar mass with palpable tender lymph nodes in the axilla. The breast was hard and swollen previously and the patient took hot baths with hot soaks to the breast. When the discharge started, the breast became smaller and the mass softer. At operation a 2 cm. cyst was found containing a papilloma measuring 1.5×1.5 cm. This undoubtedly accounted for the round quality of the shadow seen on the roentgenograms. Microscopically, the intracystic papilloma was highly cellular and the surrounding breast showed duct hyperplasia.

It should be pointed out here that a helpful sign in differentiating carcinoma, at least of the scirrhous variety, from gyn-

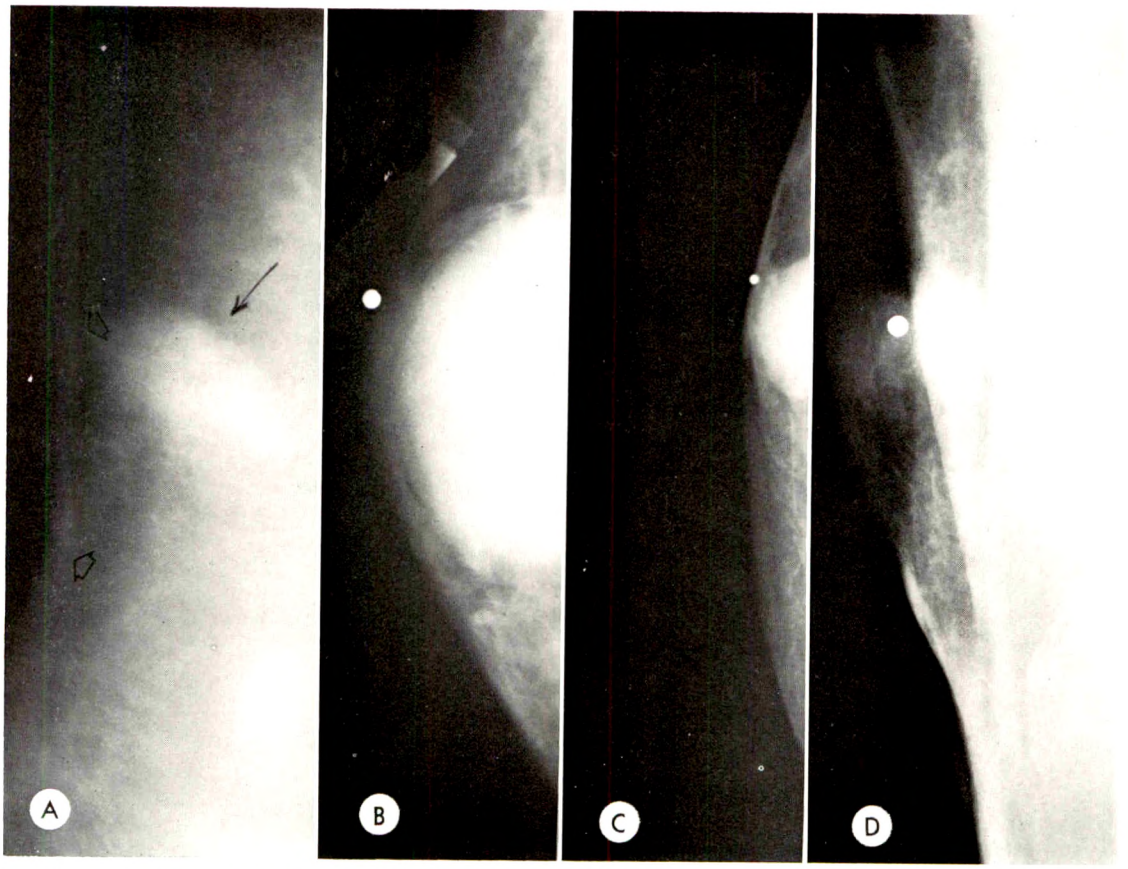


Fig. 6. (*A*) A scirrhous carcinoma. Note the flame-shaped tail at the posterior aspect of the mass (posterior arrow). This "tail" we have seen often in malignancy in female breasts, particularly in cases of medullary carcinomas and sarcomas. Secondary roentgen signs are also present: note thickening of overlying skin (lower arrow) and retraction of the nipple (upper arrow). An easily diagnosed case. (*B*) This is a large cyst which was found to contain a papillary adenocarcinoma.Several irregular densities are seen adjacent to the smooth margins of the cyst and probably represent surrounding inflammatory reaction.The carcinoma here is, of course, impossible to recognize since it is contained entirely within the cyst. (*C*) This scirrhous carcinoma was erroneously believed to be a benign lesion because of its smooth borders. The posterior margin of the mass, however, was not completely included on the roentgenogram and may have shown other suspicious characteristics had it been possible to demonstrate all its margins. This illustrates the need for attention to proper technique in performing roentgenography. A nontender mass was noted here by the patient for a period of 3 to 4 months and was believed to fluctuate in size. (*D*) This case, a scirrhous carcinoma, was thought to show changes due to inflammatory disease or hypertrophic breast tissue. Note the great similarity to Figure 6*E*, a case of inflammation. The appearance is practically identical. There is also considerable similarity to Figure 6*F* which is a gynecomastia case. The patient shown here was aware of a nonpainful, nontender lump in the breast for a period of 1 year. In retrospect, the involved area appears to be located eccentrically in relation to the nipple—a clue to its true identity?

ecomastia would appear to be the location of the lesion eccentrically in relation to the nipple or separated from the nipple. In gynecomastia, with rare exceptions such as in Figure 6*F*, the hypertrophic breast tissue tends to fan backward from the nipple to the deeper portion of the breast and to extend slightly laterally. The distribution, therefore, would generally resemble a triangle with its apex at the nipple. This sign would be of no help in a carcinoma located directly behind the nipple or in differentiating carcinoma from inflammation, however, since the latter may obviously

occur anywhere in the breast (Fig. 6, *B*, *C* and *D*).

Pitfalls in diagnosis include false positive interpretations as well as false negatives. Figure 6, *E* and *F* is an example of 2 benign cases that were mistakenly believed to be malignant in nature.

FURTHER DISCUSSION

It is of great interest, but not surprising, that abnormalities of the male breast resemble in every way those found in roentgenographic study of the female breast. The responsiveness of the male breast to hormonal influences parallels that of the female. In this regard the age incidence of disturbances of the male breast, *i.e.*, gynecomastia in particular, is easily explained by the fact that the male breast is not constantly undergoing physiologic changes during the sexually active phase of life. Thus we see gynecomastia develop during periods of hormonal imbalance or alteration and especially in adolescence and senescence, with malignancy appearing primarily in later life.

Of our 125 cases 6.4 per cent were finally proven to have cancer. Only a few of these showed the well known picture of scirrhous carcinoma with pathognomonic spicules, and it is of interest that no case had the fine calcific deposits found in 30 per cent of malignancies of the female breast. Generalizations, however, cannot as yet be made concerning these points because of the small number of carcinomas found to date. As additional carcinoma cases are accumulated, we may expect to be able to draw more substantial conclusions concerning the roentgenographic appearance of malignancy in the male breast.

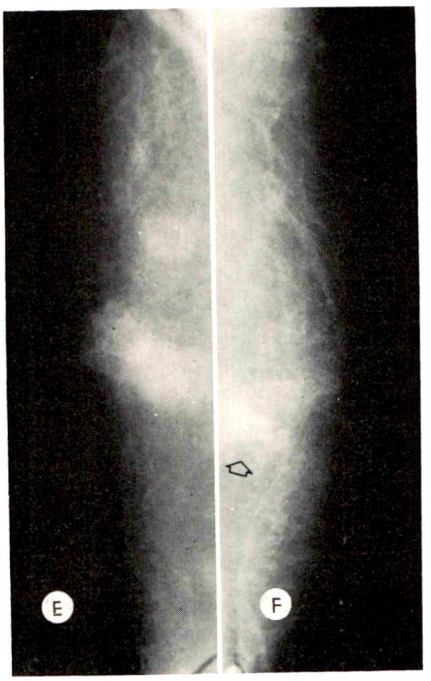


Fig. 6. (*E*) A false-positive diagnosis. This case, thought to be a malignancy, proved to be an inflammatory process. The resemblance to Figure 6*D*, a proved carcinoma, is remarkable. See note under Figure 3*B* for background. (*F*) A case of gynecomastia mistakenly interpreted as suspicious of carcinoma. Note the lack of the usual triangular, fairly symmetric distribution of hypertrophic breast tissue usually seen in gynecomastia. A pea-sized nodule was present in this breast for 1 year but began increasing in size, finally with dimpling of the skin in the 2 months prior to examination.

SUMMARY

The roentgen picture of a number of conditions affecting the male breast has been presented. The cases illustrated in this article represent the spectrum of the normal and pathologic conditions found in our clinic from 1950 to 1961.

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INTRAVENOUS PYELOGRAPHY AS A SCREENING TEST IN RENAL HYPERTENSION*

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HYPERTENSION secondary to renal vascular occlusion is a well recognized clinical entity that can be corrected by appropriate operation in the majority of cases. Definitive diagnosis for the most part depends upon the result of renal arteriography and/or differential renal function tests. Since these studies are elaborate, costly, and not without risk[1,8,18] and since only a small percentage of the general hypertensive population may have renal vascular disease,[3,4,16] the need for an effective screening test has become increasingly apparent.

Less toxic studies, such as radioisotope renography,[19] the renal scintiscan,[5] or the response to intravenous TEAC,[13] have been tried but have been found generally unsuitable as screening procedures. In the past intravenous pyelography has been reported as an unreliable screening test, normal pyelograms being found in 32–50 per cent of patients with correctable renal vascular lesions.[14,17,22]

However, with the more complete understanding of the physiologic response of the kidney to ischemia,[10,17] intravenous pyelography can be performed and interpreted in a much more meaningful way. The present study will show how intravenous pyelography can effectively be employed as a screening test in patients with suspected renal hypertension.

PHYSIOPATHOLOGY OF RENAL ISCHEMIA

In patients with significant unilateral renal vascular occlusion, blood flow to the ischemic kidney is reduced. Glomerular filtration is also decreased, and the urine therefore flows more slowly down the ischemic nephron. As a result of this, injected contrast medium may arrive in the calyces and renal pelvis later on the ischemic side,[9] particularly if roentgenograms are taken as early as 3 minutes following injection.[6] Since only roughly half of normal individuals will show a pyelogram 2 minutes after injection, a routine 2 minute pyelogram is not indicated.[12]

However, as the urine flows slowly down the ischemic nephron, water is excessively reabsorbed by the tubules and the contrast medium is thereby hyperconcentrated on the side of ischemia.[2,9,17,23] Roentgenograms taken later in the series, at 15 or 30 minutes, may then show a more dense pyelogram on the side of disease. Of course, if disease has progressed to complete arterial occlusion, little or no contrast will appear on the side of ischemia, even on long delay roentgenograms.

When ischemia is present for a period of time, ischemic atrophy of the kidney occurs. This results in a significant difference in size between the two kidneys in most cases. Segmental atrophy or infarction may produce irregularity in renal contour or distortion of the calyces in the involved segment.[21] Rapid intravenous injection of the contrast agent, with a nephrogram obtained 20 to 30 seconds later when most of the contrast material is still in the renal cortex, can be of help in evaluating renal size and contour.

Occasionally, when renal arterial occlusion is severe, collateral circulation to the renal hilus via upper ureteral vessels may develop. These vessels may become so large as to compress the upper ureter or renal pelvis and cause "notching" of these

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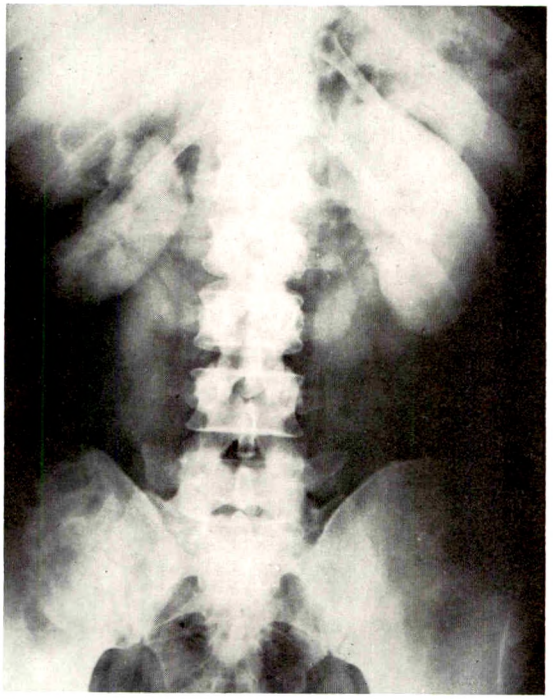


FIG. 1. Irregular renal contour demonstrated on nephrogram in patient with segmental vascular occlusion of the right kidney.

structures on the pyelogram.[20] These defects are constant in their location and should not be confused with normal peristaltic waves.

MATERIALS AND METHODS

A. PERFORMANCE AND INTERPRETATION OF THE PYELOGRAM

With the above concepts in mind, the technique of intravenous pyelography in this series of hypertensive patients included:

1. Rapid intravenous injections of contrast medium with a "nephrogram" 20 to 30 seconds after injection.
2. Pyelograms 3, 5, 15, and 30 minutes following injection.
3. Avoidance of abdominal compression which might selectively impair renal drainage.

The pyelograms were considered negative only if *none* of the following criteria were fulfilled:

1. Difference in length of 1.5 cm. or more.
2. Delay of arrival of contrast in one renal pelvis on the 3 minute pyelogram.
3. Hyperconcentration of contrast during later pyelograms.
4. Irregularity of renal contour or distortion of calyces.
5. "Notching" of upper ureter or pelvis.

Figures 1 to 5 illustrate these principles.

B. SELECTION OF PATIENTS

Intravenous pyelograms were reviewed in 35 patients with significant renal arterial disease both demonstrated by arteriography and confirmed at operation. Lesions varied from bilateral occlusion of the main renal arteries to partial occlusion of a segmental vessel. All patients had significant hypertension and 80 per cent were improved following nephrectomy or renal revascularization.

Pyelograms in 36 patients with essential hypertension were also reviewed. All patients had normal renal arteriograms. Sixteen had differential renal function studies, all of which were normal; 3 additional patients were found not to have renal vascular disease at operation or autopsy.

All of the roentgenograms were presented at random to 2 of the authors (R.C. and B.B.) who had no prior knowledge of the patients. The official radiology report on each patient's chart was later reviewed, and the results separately recorded.

RESULTS

A detailed analysis of the pyelographic findings in both groups of patients is presented in Tables I and II.

The pyelogram was found to be abnormal in 31 (89 per cent) of the 35 patients with renal vascular disease. A significant size differential (present in 57 per cent of cases) was more commonly found than any other single parameter. Differences in kidney length ranged from 5.3 cm. to 0 cm. (mean 2.1 cm., median 1.8 cm.) Incorporation of all parameters into the interpretation was necessary to obtain maximum diagnostic accuracy. The most common excretory abnormality was a delayed or less dense pyelogram of the smaller kidney. Ten

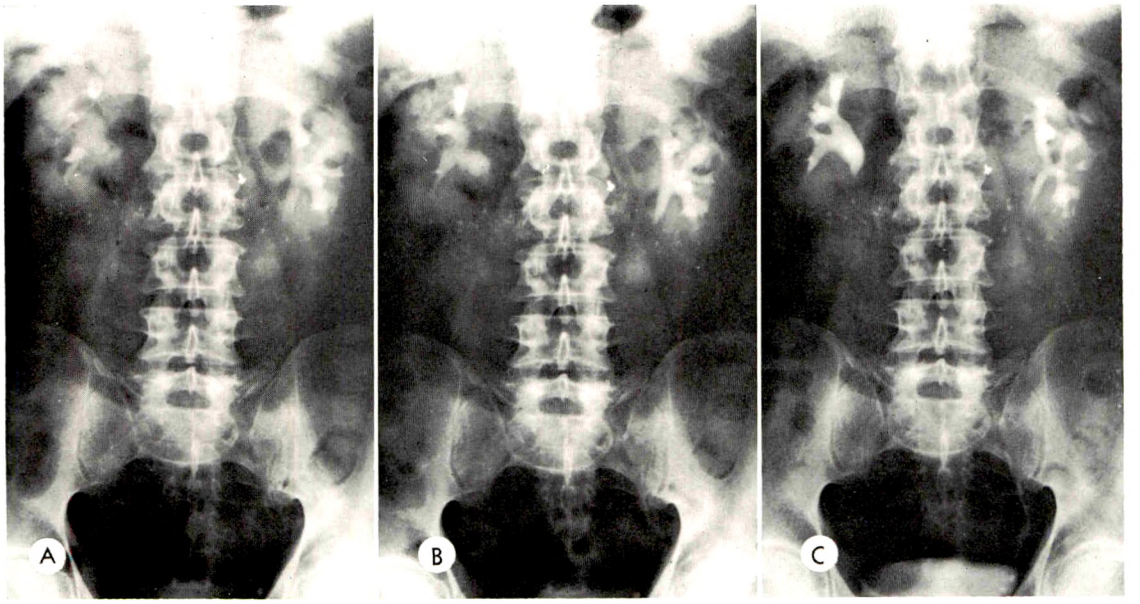


FIG. 2. (*A*, *B* and *C*) Intravenous pyelograms of a 50 year old man with arteriosclerotic occlusion of the right renal artery. Note delay in appearance of contrast medium at 3 minutes and hyperconcentration at 30 minutes on the side of the ischemia.

patients demonstrated this on the 3 minute pyelogram only, whereas in 9 more this was noted throughout the entire series of pyelograms. Only 3 patients had the "classic" findings of decreased renal size, delayed early appearance, and hyperconcentrated late pyelogram on the ischemic side. "Notching" of the ureters was noted in 3 instances. Of the 4 patients with normal pyelograms in this group, 2 had bilateral and 1 segmental arterial disease.

The pyelogram was falsely abnormal in 19 per cent of the 36 patients with essential hypertension. Differences in size in this group ranged from 0 to 1.4 cm. (mean 0.46 cm., median 0.5 cm.). Difference in concentration found only in the delay pyelogram was the most misleading parameter (4 of 7 false positive pyelograms).

The official radiology reports revealed abnormality in only 51 per cent of the patients with renal hypertension, and false positive pyelograms were found in 8 per cent of the patients with essential hypertension.

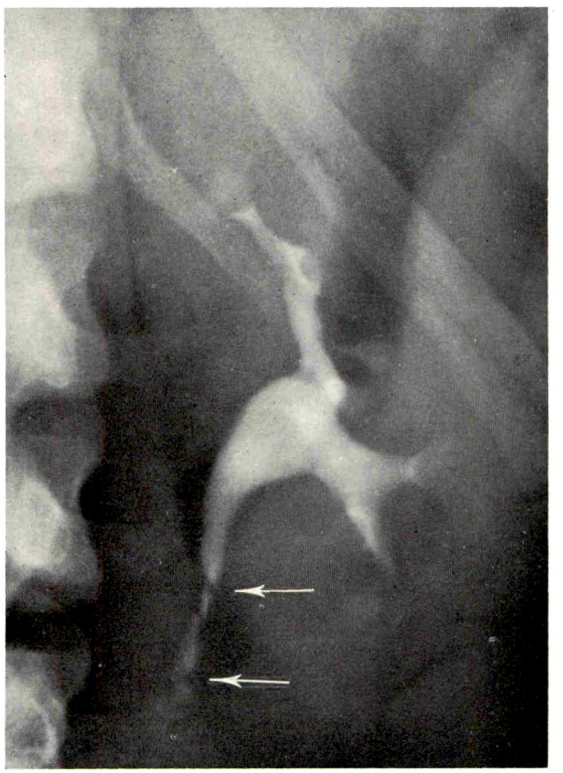


FIG. 3. Intravenous pyelogram of a 30 year old woman with high grade fibromuscular occlusion of the left renal artery. Note "notching" of upper ureter caused by collateral circulation to the kidney.

DISCUSSION

Intravenous pyelography has long been

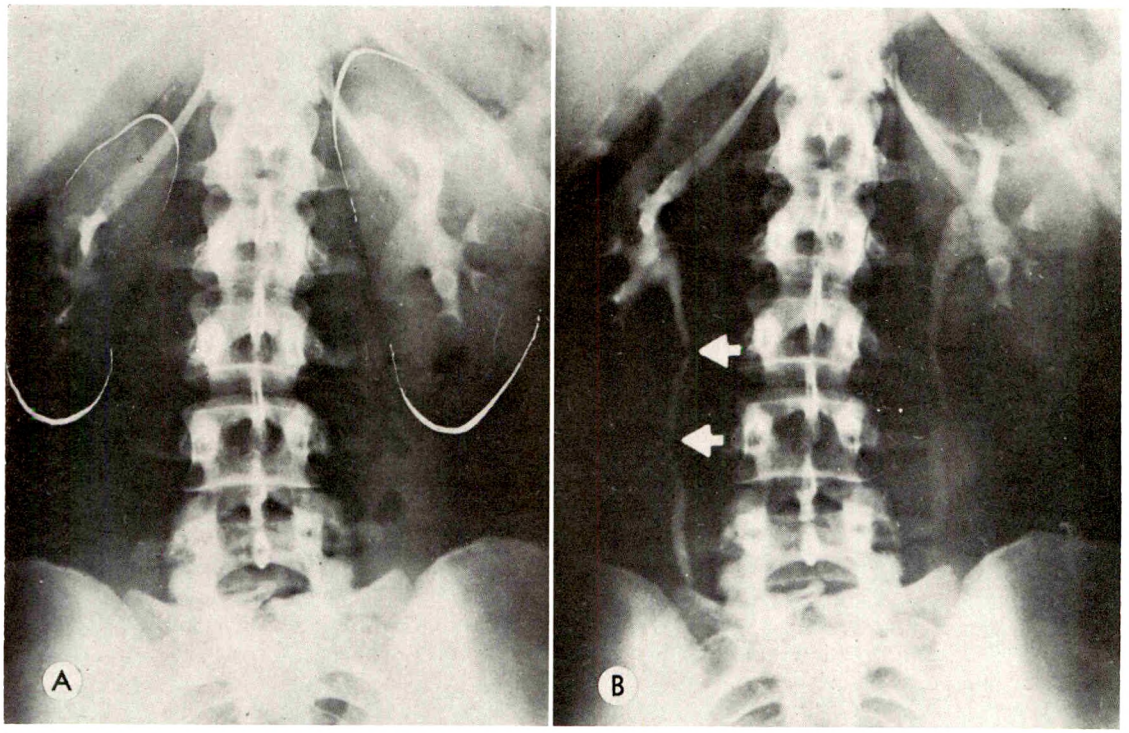


FIG. 4. (*A* and *B*) Intravenous pyelograms of a 25 year old woman with occlusion of the right renal artery. The right kidney is 2 cm. smaller than the left. While there is delay in arrival of contrast medium into the right renal pelvis at 3 minutes, there is already hyperconcentration in the upper calyx. Later roentgenograms show hyperconcentration of the entire right pyelogram with "notching" of the right upper ureter (in this case due to right ovarian artery).

maligned as a poor screening test in patients with suspected renal hypertension; however, by applying recently acquired knowledge of the physiopathologic response of the kidney to ischemia, marked improvement in both the performance and interpretation of the pyelogram is possible. Eighty-nine per cent of 35 hypertensive patients with proven renal vascular disease were found to have abnormal pyelograms by these revised criteria. Only 51 per cent of the pyelograms were reported positive on the official radiology reports in these same patients where the older, more conventional criteria of abnormality were used.

TABLE I

RESULTS OF INTRAVENOUS PYELOGRAPHY IN HYPERTENSIVE INDIVIDUALS USING EXPANDED CRITERIA OF ABNORMALITY

Patient Group	No. of Patients	Abnormal Intravenous Pyelograms	Size Differential >1.5 cm.
Renal Ischemia	35	31 (89%)	20 (57%)
Essential	36	7 (19%)	0

By employing the newer method of interpretation, the false positive rate in patients with essential hypertension also rose from 8 to 19 per cent. Yet this seems a small price to pay for the much greater increase in diagnostic accuracy in patients with renal vascular disease.

The minimum kidney length differential was arbitrarily set at 1.5 cm. By reducing this standard to 1 cm., one patient with renal hypertension and 2 with essential hypertension would have been called positive. When a duplication anomaly of the kidney is present, the size criterion is not valid.

The state of hydration may play an important role in the pattern of appearance of

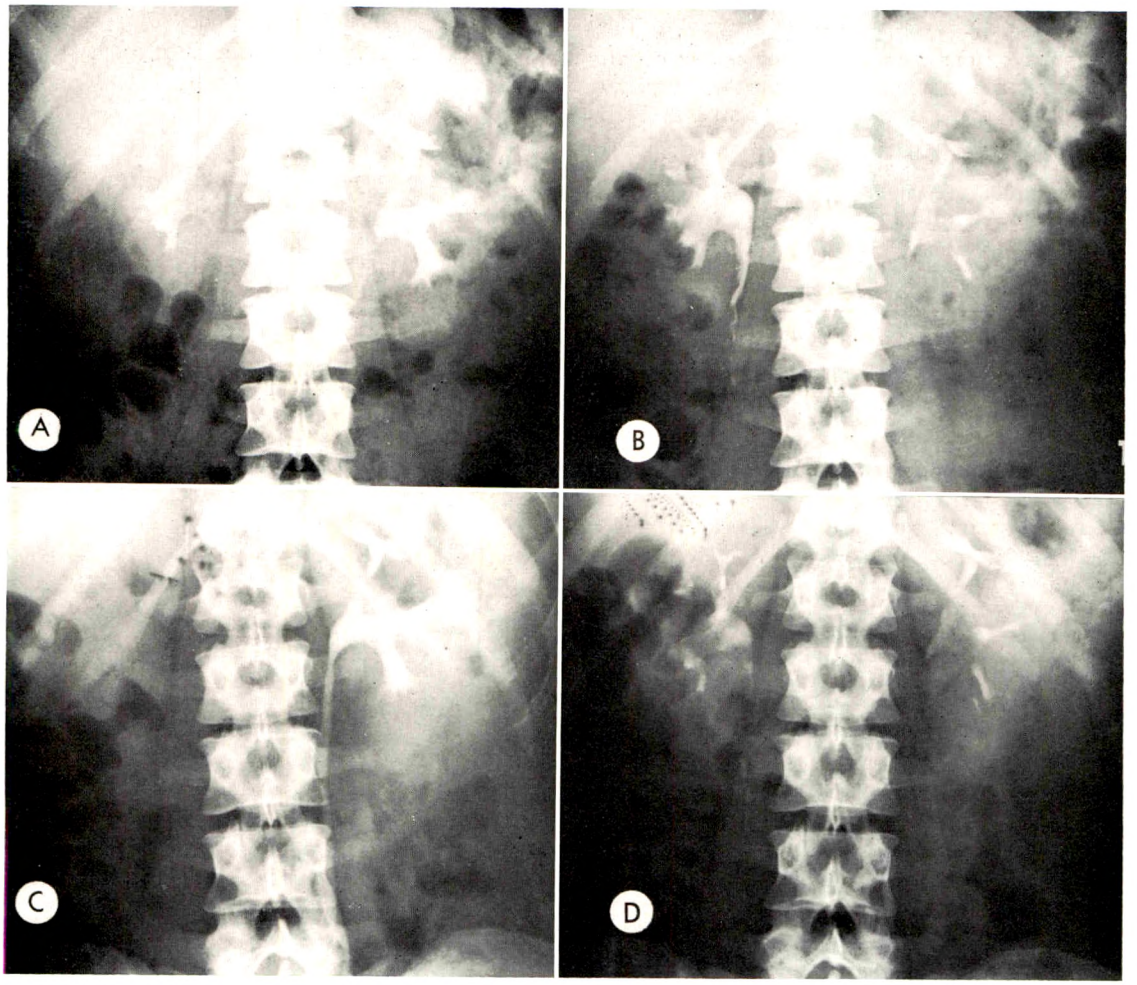


FIG. 5. (*A* and *B*) Intravenous pyelograms of a 26 year old woman with malignant hypertension due to a fibromuscular occlusion of the right renal artery. Note delay in arrival of contrast material into right renal pelvis at 5 minutes, with hyperconcentration of right pyelogram at 15 minutes. (*C* and *D*) Intravenous pyelograms of the same patient two months later. Note the absence of contrast at 5 minutes and faint concentration at 15 minutes on the ischemic side. If this disease had been allowed to progress unchecked, complete nonvisualization in the right pyelogram would probably have developed within a few months.

contrast on the pyelogram. The renal pelvis of an ischemic kidney may normally fill even on the 3 minute pyelogram in a well hydrated patient. The purposeful use of overhydration,[7,11] attempting to differentially "wash out" the contrast from the normal kidney, was not employed in this series. However, it is conceivable that this technique may reveal an abnormality in patients with renal hypertension whose pyelograms are otherwise normal.

In an occasional patient the renal pelves may vary considerably in size and shape. Interpretation of contrast medium density in these is, of course, rendered more difficult, and here one should rely more upon the density of contrast medium in the calyces and ureters.

Since some patients with correctable renal vascular disease will have a normal pyelogram, it is necessary to combine other diagnostic aids with pyelography before it can become a completely effective screening test. Proper use of certain historical and physical findings can fill this need.[3] Patients with renal hypertension often have rapidly

TABLE II

INCIDENCE OF CRITERIA FOR ABNORMALITY ON THE INTRAVENOUS PYELOGRAMS OF 35 RENAL ISCHEMIC HYPERTENSIVE PATIENTS AND 36 "ESSENTIAL" HYPERTENSIVE PATIENTS. THE ISCHEMIC KIDNEY IN ALL CASES IS CONSIDERED TO BE THE SMALLER KIDNEY EVEN WHEN THE SIZE DIFFERENCE IS NOT SIGNIFICANT

Criteria for Abnormality	Renal Ischemia	Essential
Size difference greater than 1.5 cm.	20	0
Size difference alone	4	0
Delay in arrival, ischemic kidney, on 3 minute pyelogram	10	0
Faint pyelogram, ischemic kidney, throughout entire series	9	2
Delay in appearance on early pyelogram, hyperconcentration late; "classic"	3	0
Hyperconcentration of ischemic kidney throughout entire series	2	0
Hyperconcentration of ischemic kidney on late pyelogram only	1	2
Decreased concentration in small kidney on late pyelogram only	1	2
Notching of ureter	3	0
Distortion of renal contour	1	1

progressive or malignant hypertension and may give a prior history of flank pain. Auscultation of the abdomen may reveal an audible bruit, further suggesting vascular occlusive disease. Fortunately, all of the patients with renal hypertension in this study who had normal pyelograms had either a positive history or an audible abdominal bruit. To date no patient who has had a normal pyelogram, a negative history, and absence of an abdominal bruit has been found to have surgically correctable renal hypertension. The advantages of employing this type of a screening procedure are obvious: expense and toxicity are low, and it is readily available to any physician in the average community setting.

It should be emphasized again that intravenous pyelography, properly performed and interpreted, is the most important part of this screening procedure.

SUMMARY

1. A more complete understanding of the physiopathologic response of the kidney to ischemia has brought about a revision in both the performance and interpretation of intravenous pyelography. This has resulted in a much higher degree of accuracy than previously appreciated.

2. Eighty-nine per cent of 35 hypertensive patients with proven renal vascular disease were found to have abnormal pyelograms, with a false positive rate of only 19 per cent in 36 patients with essential hypertension.

3. When combined with specific historical and physical findings, intravenous pyelography becomes an effective screening test in patients with suspected renal hypertension. Advantages of low cost, low toxicity, and universal availability are obvious.

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PYELOGRAPHY AS AN AID FOR THE DIAGNOSIS OF LIVER CIRRHOSIS

WITH A STUDY OF THE NORMAL POSITION OF THE KIDNEYS

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LIVER cirrhosis frequently runs an insidious course and may remain clinically silent until it reaches an advanced stage. Additional diagnostic indications are therefore desirable.

In 1959, Schorr and Birnbaum[6] described upward displacement of the right kidney as a diagnostic aid in liver cirrhosis. The right kidney was found to be higher than the left, and at a higher level in relation to a fixed structure, the vertebrae, in 16 out of 20 cases of liver cirrhosis of varying etiology. The right ureter was found to be straightened out in 14 of the 16 patients with a raised right kidney. It was concluded that upward displacement of the right kidney may be a helpful sign in suspected liver pathology, mainly liver cirrhosis, and a base for follow-up of the diminution in size of the liver.

These findings, while they may not always represent early liver pathology, at least, offer a diagnostic possibility and aid in many cases. In the present study further evaluation of this sign; namely, the raised position of the right kidney, is reported.

NORMAL MATERIAL AND RESULTS

In order to assess the frequency of a high right renal position as a normal developmental variant, a meticulous survey of normal excretory urograms of a group of 1,300 adult cases without evident kidney, spleen or liver disease was made. Cases with high diaphragms or scoliosis were omitted.

The comparative points in the correlated position of the kidneys were the centers of the roentgenologically visualized renal pelvis. In addition the position of the center of the renal pelvis of each kidney was correlated to landmarks in the lumbar spine; namely, the intervertebral space and the transverse process of the vertebrae.

In the group of 1,300 consecutive urograms, only 18 cases (1.3 per cent) were found with a high right kidney (Fig. 1). These patients had no history of any abdominal surgical intervention or any clinical evidence of kidney, spleen or liver disease. Thus, a right kidney situated at a higher level than the left one is an unusual finding. There were 35 possibilities of relationship between the two kidneys, of which 6 groups form a majority of 79.5 per cent (Fig. 2).

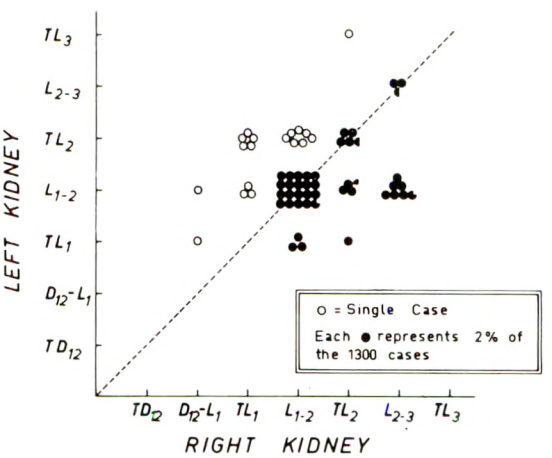


FIG. 1. Normal material. The position of the left and right kidneys on 1,300 normal intravenous pyelograms in relation to the vertebrae is shown. In 18 cases (1.3 per cent) the right kidney was higher than the left. TL_3 = Transverse process of the third lumbar vertebra. L_{2-3} = the intervertebral space between the second and third lumbar vertebrae.

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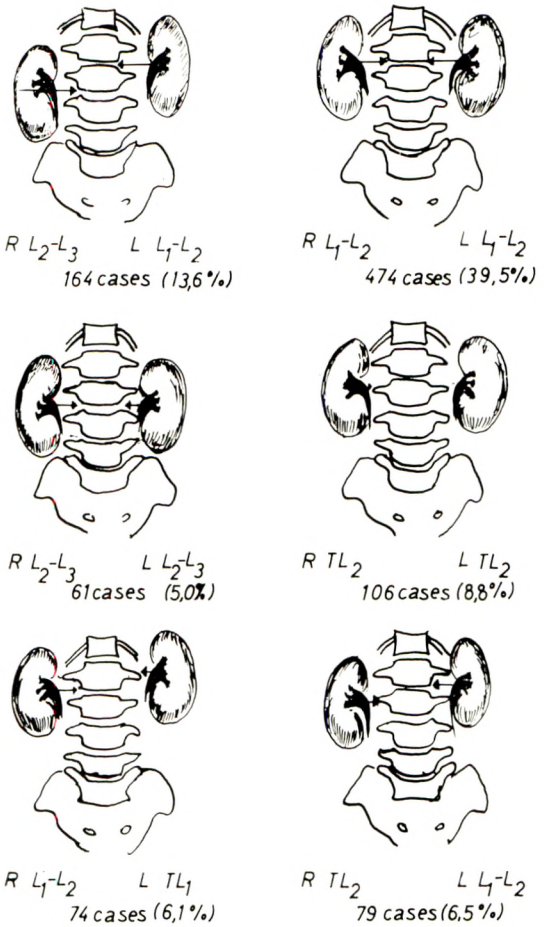


Fig. 2. Normal material. Six major groups of the 1,300 normal urograms illustrating the relation of both kidneys to each other and to the spine (79.5 per cent of 1,300 cases).

Three out of the 6 groups showed both kidneys to be at the same level; they comprise 53.3 per cent of the cases in the 6 major groups. Figure 3 shows the levels of both kidneys in the major groups.

Groups which include only several cases or atypical levels are not considered in detail.

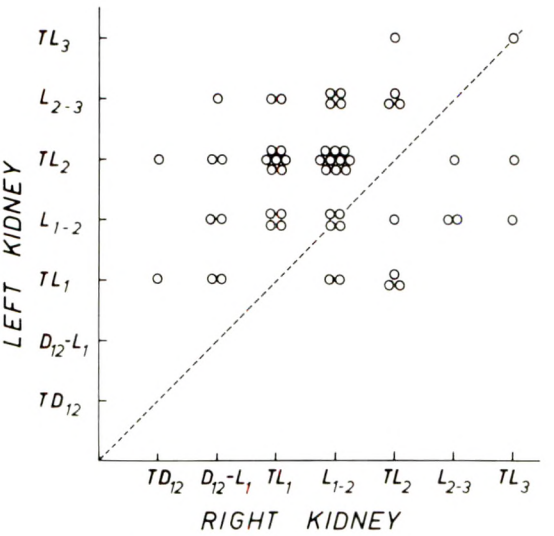


Fig. 4. Pathologic material. The position of the left and right kidneys in 56 cases of liver cirrhosis is shown (40 cases R/L, 5 cases R=L, 11 cases L/R).

Pathologic Material and Results

Fifty-six patients with cirrhosis of the liver of varying etiology who had had excretory pyelography were reviewed. Of these, in 40 the right kidney was higher than the left (R/L), in 5 cases both kidneys were at the same level (R=L), and in 11 the left kidney was higher than the right (L/R) (Fig. 4 and 5).

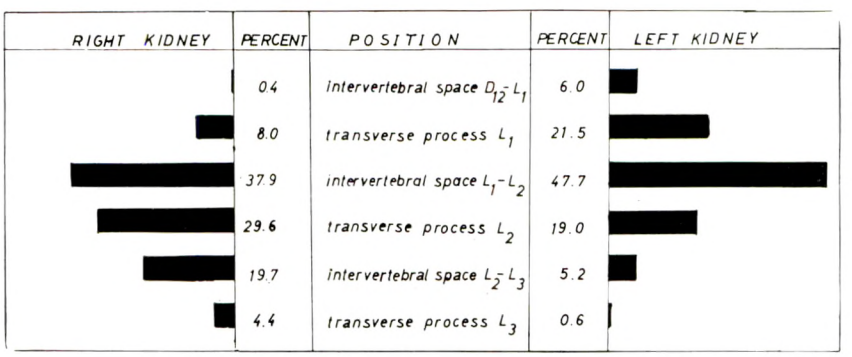


Fig. 3. Normal material. The levels of the right and left kidney in the six major groups are shown.

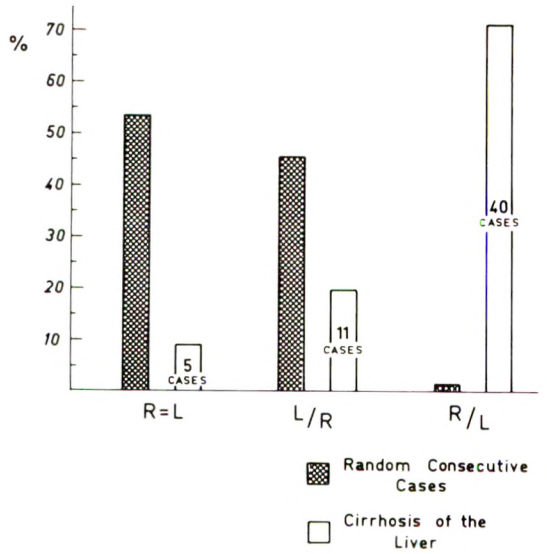


FIG. 5. Normal and pathologic material. A comparison of the 1,300 normal pyelograms with the 56 pyelograms in cases of liver cirrhosis is shown.

The relationship of the long axis of the kidney to the midline of the spine and the psoas shadow was checked. Normally the long axis of the kidney runs obliquely away from the midline at about 20 degrees and is generally parallel to the psoas shadow. In cases of elevated right kidney, the renal mass becomes more vertical, more parallel and somewhat closer to the vertebral column. When the ureter is straightened out, the long axis of the renal mass and the ureter form one vertical line.

In 5 cases the raised right kidney was confirmed at autopsy (Fig. 6), in 4 at laparotomy, and the rest were diagnosed clinically. Among the latter there were 2 cases of Wilson's disease (Fig. 7). In 3 cases, the change in the position of the right kidney (upward displacement) could be followed by successive studies and corresponded with the diminution of the size of the liver. In one case we were able to follow a normal position of the kidneys (R=L) to a raised right kidney (R/L) after 6 years and in 2 cases after 3 years. One patient (Fig. 8, *A* and *B*) was a male, aged 52, who died from a myocardial infarction on an arteriosclerotic basis. At autopsy, it was found that the dome of the right diaphragm reached the level of the fourth rib. The right kidney was elevated markedly, its lower pole being in line with the lower margin of the right hepatic lobe, 2 cm. above the right costal arch. The upper pole of the right kidney was 2 cm. below the right diaphragm and it measured 9 cm. in length, 5 cm. in width, and 3 cm. in thickness. A small cyst was noted at the lower pole. The kidney was in a state of traction toward the diaphragm, forming an angle of approximately 60 degrees with the abdominal aorta. An opaque, thin layer of connective tissue bound the renal capsule to the capsule of the cirrhotic liver as it enveloped the liver (Fig. 9). The left kidney appeared normal. The upper pole was 8 cm. below the left diaphragm.

The liver weighed 1,180 gm. It was granular and showed nodular and granular

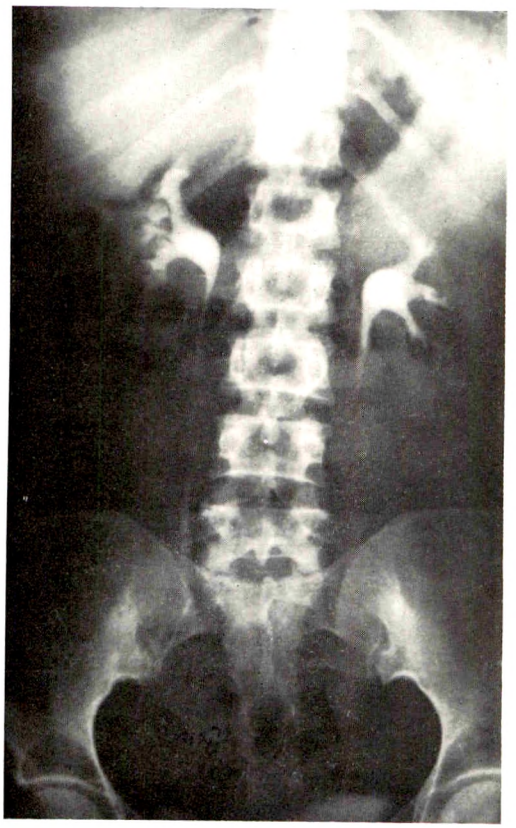


FIG. 6. Female, aged 55, with liver cirrhosis, Laennec type (R/L). The midpelvis of the right kidney is at L_{1-2}, the midpelvis of the left kidney at TL_2. Note the straightened right ureter.

masses on the cut surface, the consistency being extremely firm. Microscopically, the liver showed typical histologic changes of cirrhosis. The hepatic capsule was adherent to the right kidney by areolar tissue which contained collaginous fibers. This connective tissue partly adjoined the peritoneum and partly the renal and hepatic capsules. It showed some mild inflammatory changes.

In 23 cases the right ureter was definitely straightened. In 7 cases the right ureter was not visualized on the urograms.

DISCUSSION

Upward displacement or raised kidney refers to a normal kidney which has been elevated from its normal position. It denotes an acquired condition. High renal ectopy refers to an abnormal renal position of congenital origin. Such changes have not been discussed to any extent in the literature.

Moody and Van Nuys[4] in their study of the position of the kidneys in healthy individuals do not mention any cases of a higher situated right kidney in their series.

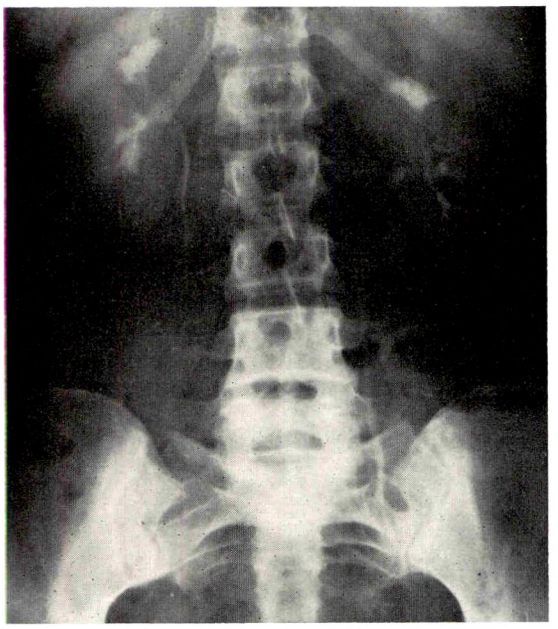


Fig. 7. Female, aged 43, with Wilson's disease (R/L). The midpelvis of the right kidney is at TL_1, of the left kidney at TL_2. Note the vertical position of the raised right kidney.

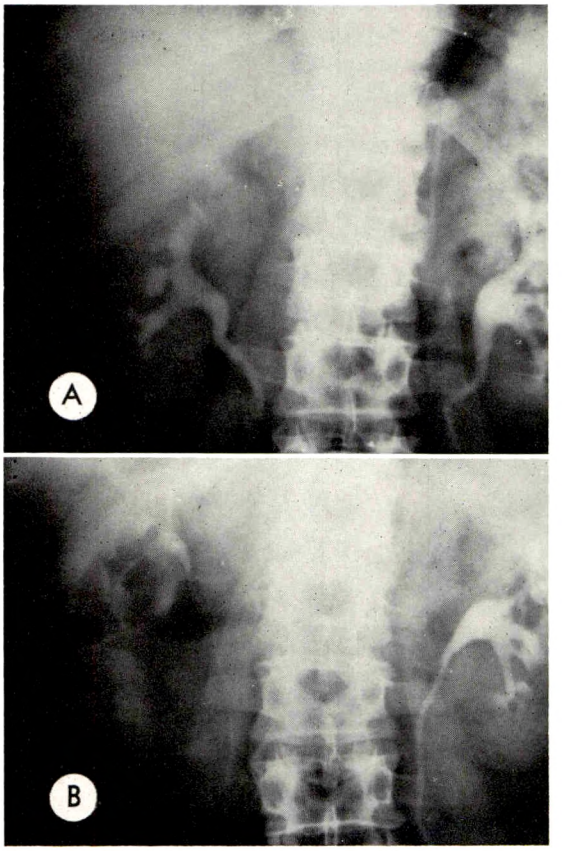


Fig. 8. Male, aged 52, with liver cirrhosis, Laennec type. (*A*) January, 1958: both kidneys are shown at the TL_2 level. (*B*) December, 1961: the right kidney is displaced upward at the L_{1-2} level; the position of the left kidney is the same.

McClellan[3] reviewed 1,500 consecutive urograms and found that the left kidney was lower than the right in 106 patients. McClellan associated the low position of the left kidney with disease or anatomic abnormalities in 29 instances, leaving 77 cases unexplained. Thus, the left kidney was considered normally lower than the right in 5.1 per cent of cases.

Forde *et al.*[2] in a survey of 100 consecutive urograms found 5 instances in which the left kidney was lower than the right. The displacement was always of minor degree and in 3 patients could not be explained except as a developmental variant. In the other 2 instances, the left kidney appeared low because of scoliosis.



FIG. 9. Gross specimen of kidney and liver showing the connective tissue capsule which pulls the kidney up toward the liver. This also shows the characteristic granular and nodular appearance of the cirrhotic liver.

Muschat and Edeiken[5] in their study of renal displacement by adjacent organs do not mention at all the possibility of a raised right kidney.

Yates[7] discussed the distortion of the pyelogram by external lesions such as liver abscess. Of 3 cases that he recorded, in one he found the right kidney to be higher than the left.

Fishback[1] in his work on renal dystopia due to intraabdominal masses reviewed the literature. He described cases of renal displacement caused by an enlarged spleen, retroperitoneal masses and an enlarged liver only.

In the 9 cases reported here, which were confirmed either at autopsy or by surgery, adhesions were found between the capsule of the liver and the fatty capsule of the right kidney. With the development of such adhesions, it is conceivable that the kidney could be drawn upwards. However, in cases where the liver turned out to be palpable and enlarged, there was also definite forward elevation of the kidney suggesting that a different mechanism must have been responsible. It may be that under such circumstances forward rotation of the liver occurs; this would result in an elevation of its inferoposterior surface with a drawing upwards of the hepatorenal ligament and thus the right kidney.

CONCLUSIONS AND SUMMARY

In 40 out of 56 cases of cirrhosis of the liver of varying etiology, the right kidney was found to be higher than the left and at a higher vertebral level.

The right ureter was found to be straightened in 23 of the cases in which the right kidney was raised.

In a control series of 1,300 normal urograms, the right kidney was found to be higher than the left in 1.3 per cent of the cases only.

It is suggested that the finding of an elevated right kidney, especially with a straightened ureter, may be indicative of liver cirrhosis and may serve as a useful diagnostic sign to substantiate the clinical diagnosis.

Our experience with a group of cases justifies certain generalizations: An elevated right kidney should be sought for by plain roentgenography and intravenous pyelography specifically ordered in cases of doubtful liver pathology, especially where cirrhosis of the liver is suspected. Intravenous pyelography in the diagnosis of cirrhosis of the liver should be considered as corresponding to an examination of the esophagus for varices.

A normal intravenous pyelogram in cases of liver cirrhosis may serve as a base line from which to judge the elevation of the right kidney. This seemingly minor finding may be an important clue to the correct diagnosis. It must be emphasized that the roentgen evidence is supplementary to the clinical picture.

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The authors wish to express their thanks to Drs. J. Munk and A. Friedman for furnishing clinical and operative findings in some cases and to Dr. E. Levy for the autopsy material.

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ARTERIOVENOUS FISTULA OF THE RENAL VESSELS*

A CASE REPORT

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BECAUSE of the rarity of arteriovenous fistula of the renal vessels, the following case is reported to add to the sparse literature of this entity. There are 26 cases reported in the literature (Table I) and 11 of these were diagnosed preoperatively by means of angiography.[5,7,13,15,16,19,21–25] The present case represents the twelfth one diagnosed by this means and is also interesting from the point of view of the urologic picture which simulated a neoplasm.

REPORT OF A CASE

The patient was a 50 year old white housewife admitted to Georgetown Hospital for the evaluation of a "back murmur." In 1953, she had an operation for a cyst in her left breast. At that time she was refused insurance because of a heart murmur. The electrocardiogram was normal. In 1958, she developed left chest pain and since that time she had noted moderate shortness of breath, dyspnea on exertion, and slight ankle edema. She also had epigastric distress, unrelated to food. In December, 1959, her family physician noted a murmur in her back for the first time.

Physical examination revealed a blood pressure of 135/80. The cardiac and respiratory rates were normal. The lungs were clear to auscultation and percussion. There was a Grade IV machinery type constant murmur heard over the left back with greatest intensity over the twelfth rib. The murmur was not obliterated by pressure. A thrill was also palpable over this area. Cardiac auscultation revealed a Grade II systolic murmur at the left sternal border and in the apical region.

Her past history revealed that she had a tonsillectomy at the age of 10, appendectomy at the age of 16, and a laparotomy for a tubal pregnancy at the age of 23. She had superficial injuries to the extremities when hit by a car but never had chest or abdominal trauma.

The routine laboratory studies showed a hematocrit of 37 per cent. The white blood cell count was 6,000 with a normal differential. Urinalysis revealed a specific gravity of 1.015, albumin was 1+, 0–2 white blood cells per high power field, and 1–2 red blood cells per high power field. Serology was nonreactive VDRL. Blood urea nitrogen was 8 per cent. The electrocardiogram showed a digitalis effect with left ventricular hypertrophy.

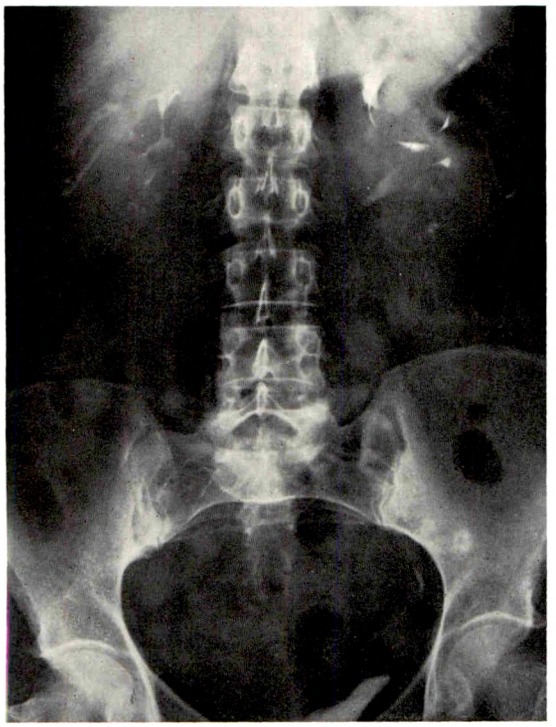
The arterial oxygen saturation was 97.6 per cent and 95.3 per cent which was evidence of decompensation.

TABLE I

CASES OF ARTERIOVENOUS FISTULA OF THE RENAL VESSELS REPORTED IN THE LITERATURE

Author	Year	Origin
1. Varela[26]	1928	congenital
2. Rieder[20]	1942	congenital
3. Pearse and MacMillan[17]	1947	congenital
4. Adams[1]	1951	congenital
5. Schulze-Bergman[22]	1954	congenital
6. Slominski-Laws *et al.*[24]	1956	congenital
7. Bohne and Henderson[3]	1957	congenital
8. Edsman[5]	1957	congenital
9. Hoffman and Fontura[10]	1958	congenital
10. Sauter and Sargent[21]	1960	congenital
11. Thomas *et al.*[25]	1962	congenital
1. Vest	1954	traumatic
2. Pelot *et al.*[18]	1954	traumatic
3. Baron and Koenemann[2]	1955	traumatic
4. Kirby *et al.*[13]	1955	traumatic
5. Milloy *et al.*[14]	1958	traumatic
1. Hollingsworth[11]	1934	postnephrectomy
2. Schwartz *et al.*[23]	1955	postnephrectomy
3. Muller and Goodwin[15]	1956	postnephrectomy
4. Dubost and Mathis[4]	1956	postnephrectomy
5. Poutasse[19]	1957	postnephrectomy
6. Harbison *et al.*[9]	1960	postnephrectomy
7. Gokarn and Swinney[7]	1962	postnephrectomy
1. Hamilton *et al.*[8]	1953	carcinoma
2. Myhre[16]	1956	carcinoma
3. Jantet *et al.*[12]	1962	carcinoma

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A plain roentgenogram of the abdomen showed a large left renal shadow. No calcifications were noted.

The excretory urogram (Fig. 1) revealed normal and prompt excretion bilaterally. The right kidney appeared normal. The left kidney showed an impression and displacement of the superior calyx and pelvis, suggestive of either a tumor or cyst. The diameter of this round, smooth-bordered lesion was 4.2 cm. Both ureters were normal.

Renal arteriography was performed by inserting a No. 10 NIH catheter into the right femoral artery (Fig. 2, *A* and *B*). The catheter was localized at the level of the renal arteries and 50 per cent hypaque was injected. The

FIG. 1. Urogram showing a smooth-bordered, round impression in the superior pole of the left kidney displacing the superior calyx and pelvis.

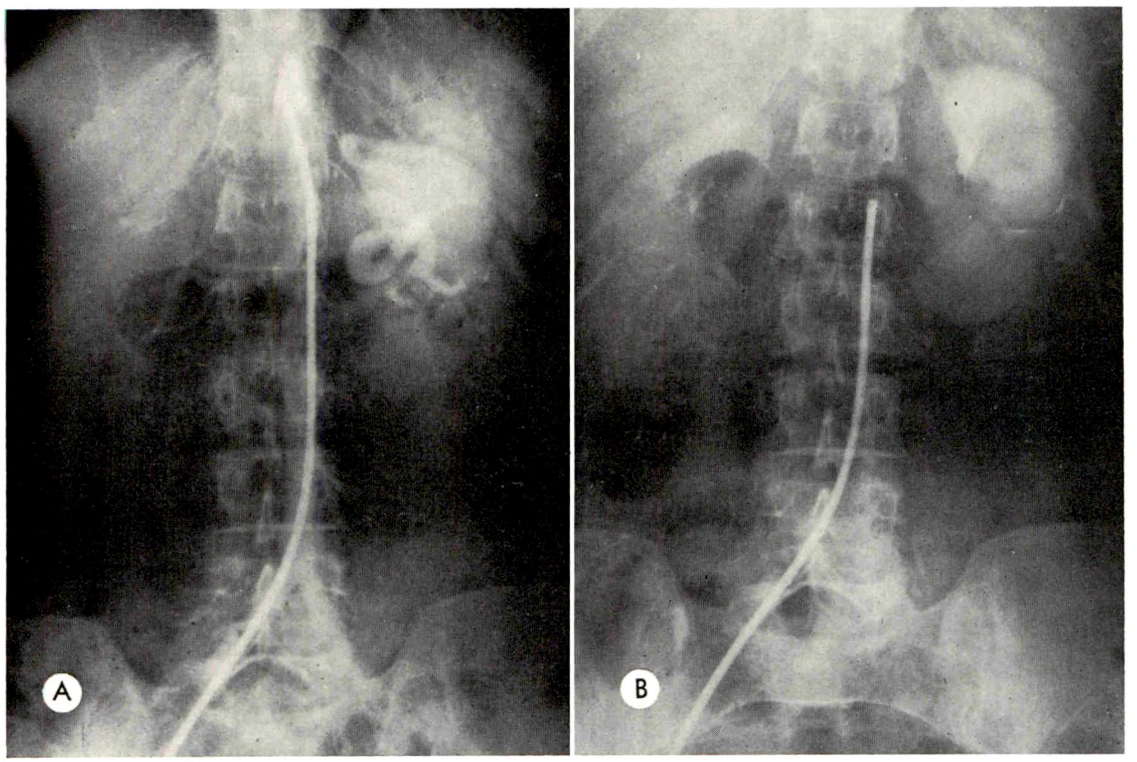


FIG. 2. (*A*) Retrograde femoral arteriogram with the tip of the catheter at the level of the first lumbar vertebra. The arterial phase shows a dilated left renal artery with tortuous dilated branches which seem to enter a large pool of contrast material in the superior pole. The kidney has an irregular shape. (*B*) Nephrographic phase showing a large pooling of medium in the superior pole which displaces and compresses the superior and middle calyces.

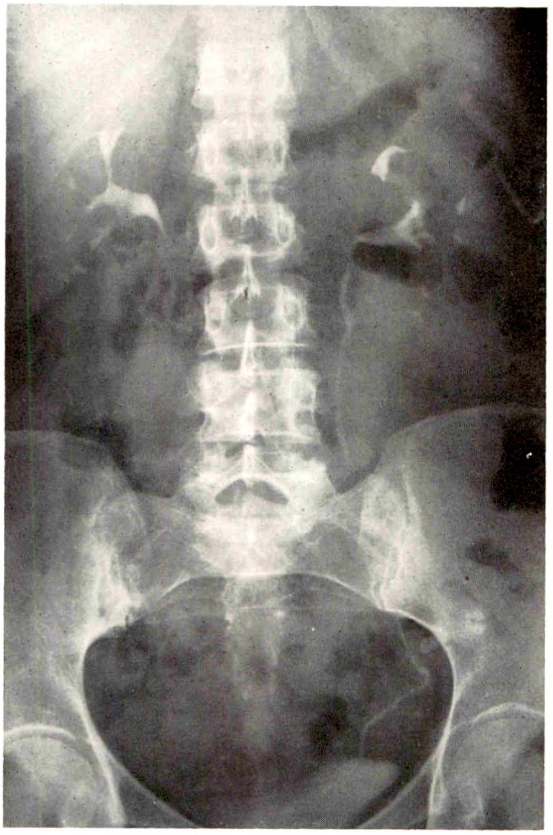


FIG. 3. Repeat urogram 10 days after operation. The calyces are well outlined and the previously observed round impression is absent. The kidney has returned to a normal shape.

aortogram showed a large arteriovenous malformation involving the left renal vessels. There was noted to be a large pooling of contrast material in the region of the superior pole of the left kidney. This produced the cystic impression on the collecting system as found on the urogram.

Under general anesthesia and hypothermia, exploration of the left kidney disclosed an arteriovenous fistula in the upper pole of the left kidney. By sharp and blunt dissection, the left kidney was completely explored. The main middle artery was found to bifurcate into two distinct branches supplying the middle and inferior portions of the left kidney, and a much larger one was found to be running into the fistula. The renal vein draining this was 3.5 cm. in diameter. That portion of the left renal artery supplying the fistula was doubly ligated. The venous component promptly decompressed. The saccular portion of the arteriovenous fistula was opened at the point where it came to the surface in the upper lateral portion of the left kidney. When the entire sac was opened, it was found to have two or three small areas where blood leaked into the sac. These were ligated. The excess portion of the sac down to good renal parenchyma was then excised and the hilar portion which was endothelized was left in position without being closed or specifically drained. Gerota's fascia was closed and a drain was left in place. The patient withstood the procedure well and had an uneventful recovery.

Ten days after operation, the urogram (Fig.3) showed a normal excretion bilaterally. The previously visualized round impression on the left pelvis and superior calyces was no longer present. The superior calyx was slightly elongated and displaced medially. A postoperative chest roentgenogram showed a decrease in heart size.

DISCUSSION

Arteriovenous fistula of the renal vessels is a rare malformation which may be congenital or acquired in origin. Of the 26 cases in the literature (Table 1), 11 have been considered congenital. Several of these have been secondary to an aneurysm with erosion through an adjacent vessel.

A definite traumatic history was recorded in 5 cases.

Seven cases developed following nephrectomy and the remaining 3 were secondary to carcinoma. There was no significant sex predilection, and the age range was from 3 to 69 years. It is noted that 10 of the patients were below the age of 30.

Hypertension was present in about half of the cases and was frequently associated with congestive heart failure. There was usually a dramatic response following operation with the blood pressure returning to normal. A bruit or thrill was the chief clinical finding and hematuria was present in 6 cases.

The pyelogram showed varying degrees of calyceal and pelvic distortion which were not pathognomonic. A definitive diagnosis can be made by aortography as was done in 12 cases including the one reported in this paper.

SUMMARY

A case of arteriovenous fistula of the renal vessels is presented.

The urographic picture simulated a renal tumor or cyst. A preoperative diagnosis was made by means of angiography.

The literature on this condition is briefly reviewed.

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We gratefully acknowledge Dr. Stanley Silverberg for his permission to report this interesting case.

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OSTEOSCLEROSIS IN CHRONIC RENAL DISEASE*

REPORT OF 4 CASES ASSOCIATED WITH SECONDARY HYPERPARATHYROIDISM

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ROENTGEN recognition of bone changes associated with renal disease is usually concerned with the following: rachitic-like findings in children afflicted with congenital enzymatic defects and signs of hyperparathyroidism. The latter may be found in children and adolescents but are usually first observed in adults with longstanding pyelonephritis and glomerulonephritis, polycystic disease, and obstructive abnormalities. The rachitic findings have been well described in the literature. Bone changes in hyperparathyroidism, either primary or secondary, have likewise been extensively discussed and, in fact, comprise a pathognomonic complex. A third abnormality, osteosclerosis, either localized or diffuse, may also be present, with or without the roentgen signs of hyperparathyroidism. Indeed, this extensive proliferation of bone may at first appear so paradoxical as to evoke doubt about a diagnosis of hyperparathyroidism.

Because osteosclerosis in association with secondary hyperparathyroidism has not been widely reported in the radiologic literature, 4 hitherto unreported cases are presented in this article. They are followed by a review of the literature, including comparison of pertinent facts about the current cases and those of others. Suggested mechanisms of development, roentgenographic findings, and differential diagnosis are also discussed.

REPORT OF CASES

CASE 1. M.J., S.M.H. Unit Number 25-97-06. Between 1947 and 1953, this Negro widow, aged 53 at the time of her death in 1953, was treated frequently in the accident wards of local hospitals for minor injuries received while intoxicated. Several roentgen examinations of various skeletal structures were negative. During an admission elsewhere for alcoholism in April, 1952, a hemoglobin of 7 gm. per 100 cc. and a blood urea nitrogen of 62 mg. per 100 cc. were discovered. The patient left that institution before additional studies could be obtained.

In May, 1953, the patient came to the emergency department of Strong Memorial Hospital because of a scalp laceration. Preliminary examination revealed a severe anemia, and the patient was admitted for evaluation. No satisfactory history could be elicited because of her persistently belligerent, surly attitude. Positive physical findings included right flank tenderness, an inflamed cervix with mucopurulent discharge, an aortic systolic murmur, and conduction deafness in the right ear. Blood pressure was 160/90. A test for sickle cell anemia was negative. A cervical culture revealed *Neisseria gonorrheae*. A urine culture could not be obtained because the patient refused to cooperate.

Roentgenograms (Fig. 1, *A–C*) demonstrated coarsening of trabeculae and increase in density of the ribs, thoracolumbar vertebrae, pelvis, and proximal femora. Sclerosis appeared most prominent about the superior and inferior borders of the vertebral bodies. Roentgenograms of the hands revealed resorption of subperiosteal bone along the lateral borders of the middle phalanges. A dental study was interpreted as showing the lamina dura to be absent in some areas and of extremely poor quality in others.

The patient was treated with penicillin and given two units of blood. Her anemia was considered most probably attributable to the renal disease. However, she adamantly refused further studies and signed out of the hospital.

She returned in September, 1953, acutely ill, with recurrent right flank tenderness, fever, dehydration, and confusion. Laboratory data confirmed acidosis and azotemia. The patient

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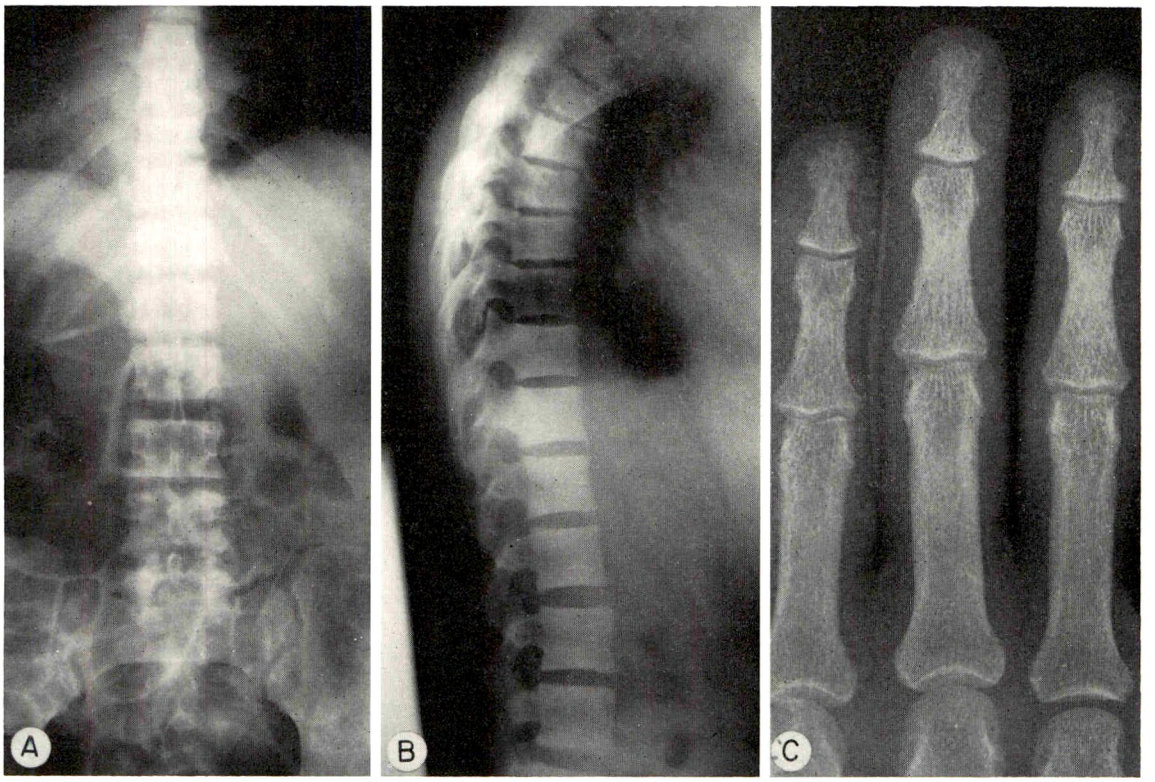


Fig. 1. Case 1. (*A* and *B*) The thoracolumbar vertebrae, ribs, and pelvis are osteosclerotic. *B* demonstrates densest bone about the vertebral end plates. (*C*) Subperiosteal resorption, characteristic of hyperparathyroidism, is present along the radial margins of the middle phalanges.

improved rapidly following administration of sodium lactate and antibiotics. A regimen of citric acid, calcium gluconate, and vitamin D was then begun. Soon, however, she again rejected all medication and left the hospital against advice.

In December, 1953, she was re-admitted semicomatose, following several weeks of vomiting, epistaxis, and progressive lethargy. Kussmaul respirations and uremic frost were evident. Despite intensive therapy to relieve severe acidosis and hypocalcemia, she remained stuporous and expired 11 days following admission.

At autopsy, contracted kidneys, "with literally no normal parenchyma," were found. A histologic diagnosis of acute and chronic pyelonephritis was subsequently made. Specimens of lumbar vertebrae and ilium revealed dense osteosclerosis. The microscopic appearance of the bone is shown in Figure 1*D* as compared to normal bone (*E*). All parathyroid glands were hyperplastic.

Case 11. F.D., S.M.H. Unit Number 43-64-04. This white boy experienced his first known urinary infection at the age of 4. This cleared promptly with sulfonamide therapy. An incidental finding was a fistula which opened on the ventral surface of the penis behind the corona. This allegedly had resulted from circumcision. No instrumentation had ever been performed.

In September, 1948, when the patient was 12 years old, urologic attention was first sought because of weight loss and intractable pyuria. A hemoglobin of 10.5 gm. per 100 cc. was noted, and blood urea nitrogen measured 61 mg. per 100 cc. *Escherichia coli* was isolated in a urine culture. Cystoscopy revealed contraction of the bladder neck and chronic cystitis. Retrograde pyelograms demonstrated advanced bilateral pyelocaliectasis and ureterectasis. No indigo carmine was recovered 1 hour following injection.

In April, 1949, a median bar contracture was resected transurethrally. During the following year, nitrogen retention did not decrease, and

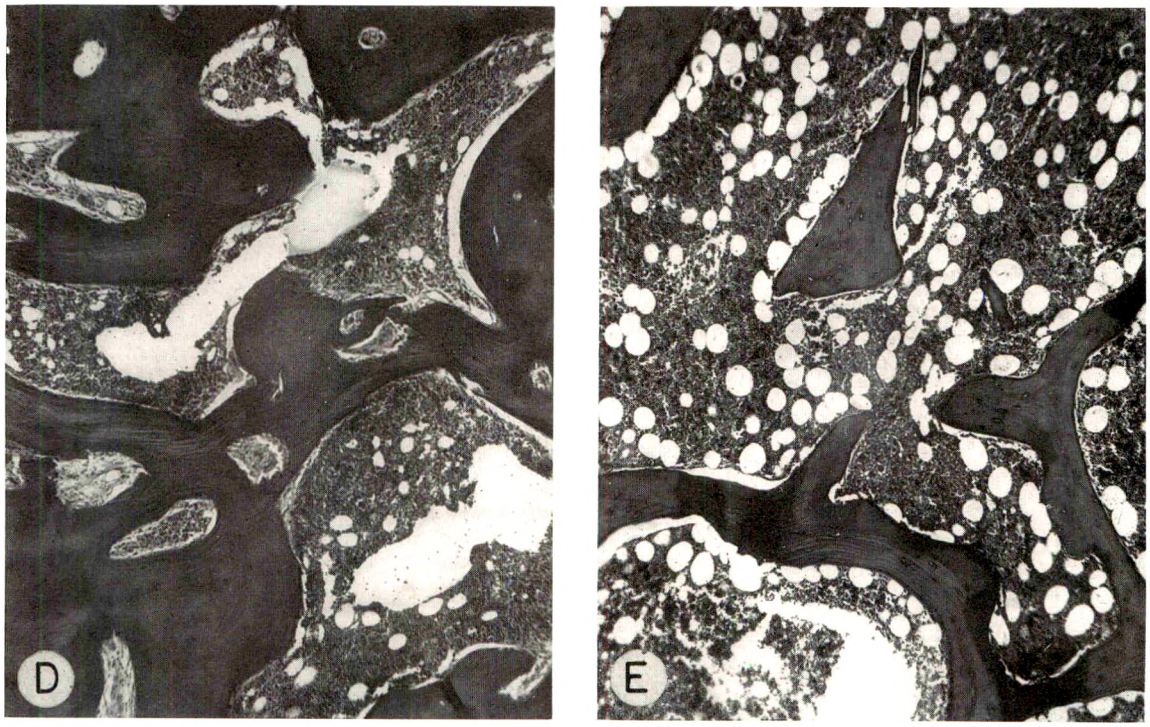


Fig. 1. Case 1. (*D*) A photomicrograph of a specimen of lumbar vertebra obtained at autopsy shows an extremely thick network of widened trabeculae. Several osteoclasts in lacunae are seen. (*E*) Bone from a lumbar vertebra of a 53 year old woman without systemic disease is included for comparison (magnification, 50 ×).

pyuria persisted, although lessened.

By February, 1954, blood urea nitrogen and serum creatinine had risen significantly. A tight ring of tissue was again observed about the circumference of the vesical neck. The volume of residual urine consistently measured 90–120 cc. A cystometrogram revealed a bladder with a capacity of 550 cc. and relatively good expulsile power. A suprapubic cystostomy was performed and utilized for 6 months. In July, 1954, a second resection of the vesical neck was performed. However, no improvement in renal function occurred following the establishment of constant drainage. Despite this, the patient remained well as the result of symptomatic therapy, including an infrequent transfusion, and was able to work full time as a bank clerk.

Fatigue, anorexia, and frequent epistaxis first became troublesome in the early months of 1957. In April, 1957, he noted enlargement of the terminal portions of his fingers and tenderness over interphalangeal joints. Two months later, because of progressive uremia and acidosis, the patient was admitted to Strong Memorial Hospital. Physical examination was negative aside from pallor, swelling of the fingers,and penile fistula. Blood pressure was 120/70. Various roentgenograms made at this time are shown in Figure 2, *A–D*. A retrograde pyelogram again revealed extensive dilatation of collecting structures and a very large bladder. A roentgenogram of the hands demonstrated advanced subperiosteal erosion of middle phalanges and a remarkable nearly total destruction of the shafts of the distal phalanges. Larger blood vessels and several joints exhibited metastatic calcification. The calvarium presented a bizarre "woolly" appearance, resulting from diffusely intermixed areas of bony resorption and proliferation. On a lateral roentgenogram of the thoracolumbar vertebrae, striking sclerosis was noted about the end plates of the bodies. These zones contrasted with the intervening porous bone. The osteosclerosis could not be appreciated in anteroposterior roentgenograms, in which vertebral densities appeared generally unchanged from studies dating back to 1948.

The patient was treated with a low-protein, alkalinizing diet, increased fluids, and several transfusions. He was discharged as improved.

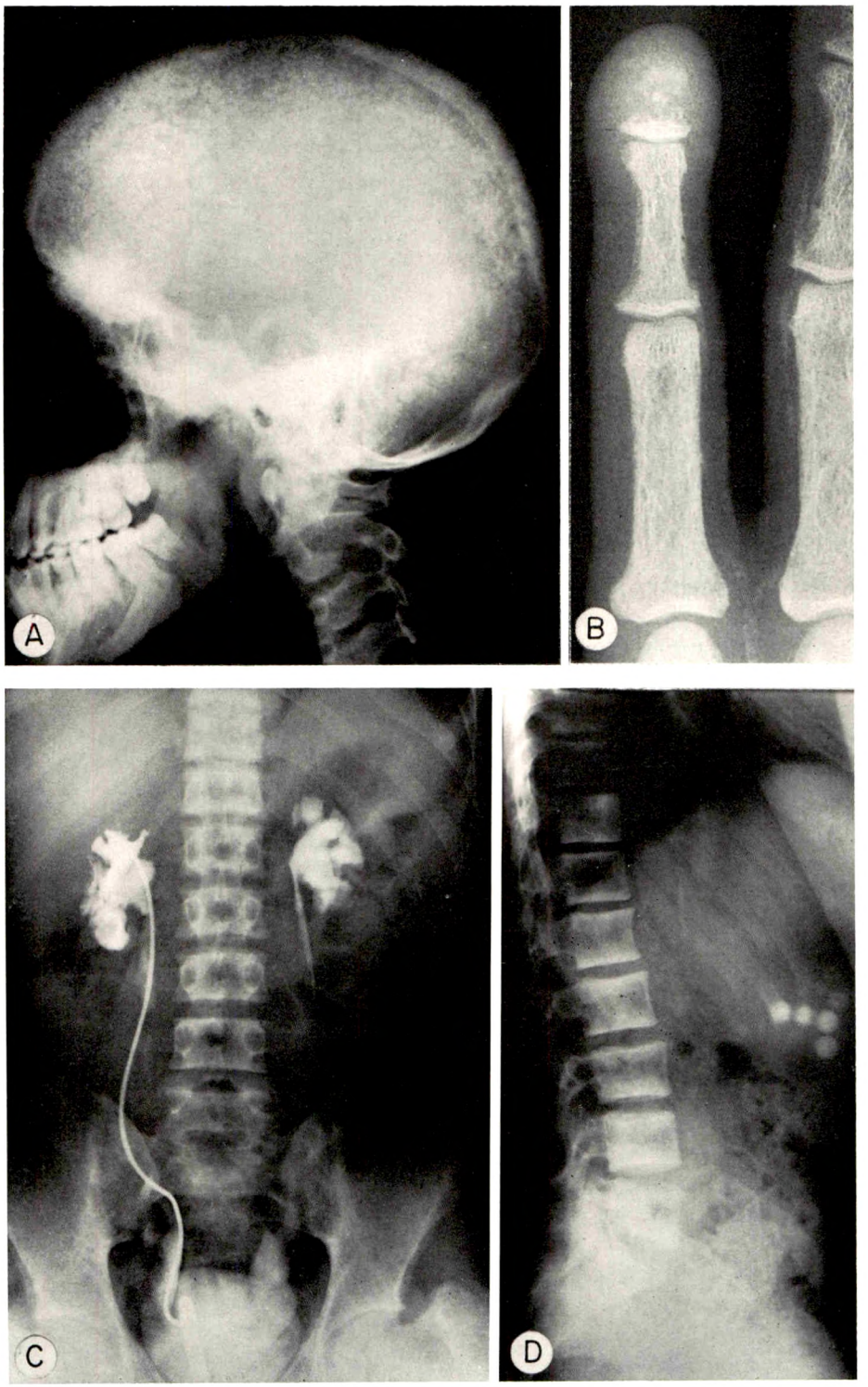


Fig. 2. Case 11. (*A*) Intermixed areas of sclerosis and resorption produce a bizarre "woolly" appearance of the calvarium. (*B*) In addition to advanced subperiosteal erosion of the proximal and middle phalanges, there is unusual destruction of the shafts of the distal phalanges. Vascular calcification is present. (*C*) A retrograde pyelogram demonstrates pyelocaliectasis and ureterectasis. Osteosclerosis of the veretebrae cannot be well appreciated on the anteroposterior roentgenogram. (*D*) A striking "rugger-jersey" effect is shown in the lateral projection.

However, he was re-admitted in September, 1957, with severe acidosis, anemia, and azotemia. In October, congestive heart failure became evident, and in November, a pericardial rub was heard. He died at the age of 21, in December, 1957. An autopsy was not permitted.

Case III. M.M., S.M.H. Unit Number 28-88-15. This white housewife's initial infection of the urinary tract occurred in 1944, at the age of 23. The symptoms readily subsided following sulfonamide therapy. According to her history, similar episodes, however, had recurred "about once a year." Her first pregnancy, in 1947, was without incident. Nevertheless, a second pregnancy, in 1954, was complicated by vomiting, acute flank pain, and increasing proteinuria. Early induction of labor was necessary. Anemia was discovered at this time.

Following this pregnancy, her health never returned to normal. Although the anemia partially responded to hematinics, the patient experienced gradually increasing malaise, weakness, and anorexia. Frequency and nocturia were also reported.

In December, 1959, the patient was first seen by the Hematology Service at Strong Memorial Hospital. Physical examination was negative except for pallor. Blood pressure was 115/80. Hematocrit was 21 per cent, and blood urea nitrogen was 87 mg. per 100 cc. Studies of peripheral blood and bone marrow revealed nonspecific hyperplasia, and the anemia was considered secondary to chronic renal insufficiency. *E. coli* was cultured from urine, and tetracycline was administered. No significant improvement ensued. Although the hematocrit rose temporarily, nitrogen retention likewise increased. Because of the latter finding as well as increasing fatigue and epigastric distress, the patient was hospitalized in May, 1961. Secondary hyperparathyroidism was suspected, and roentgenograms (Fig. 3, *A–F*) confirmed subperiosteal erosion along the lateral borders of the phalanges of the hands, plus spotty areas of diminished density in the skull. The lamina dura was largely absent, and there was resorption of adjacent alveolar bone. No calculi or soft tissue calcification was noted. Although bones had appeared normal on a 1957 pyelogram, current roentgenograms revealed striking sclerosis of the ribs, thoracic and lumbar vertebrae, and pelvis. A gastrointestinal study was negative. The symptoms improved following antacid therapy and transfusions.

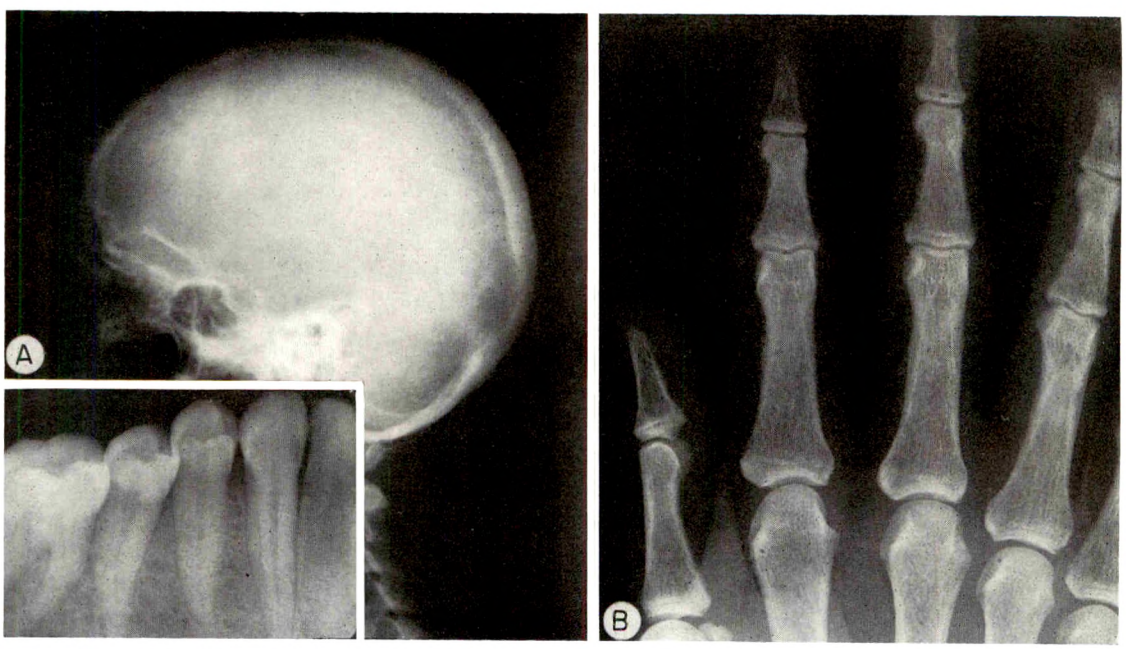


Fig. 3. Case III. (*A*) The calvarium exhibits the typical diffuse, spotty, granular demineralization, associated with hyperparathyroidism. Dental roentgenogram (inset) reveals resorption of the periodontal membrane, with resulting loss of the lamina dura. (*B*) Extensive subperiosteal erosion involves the middle and distal phalanges.

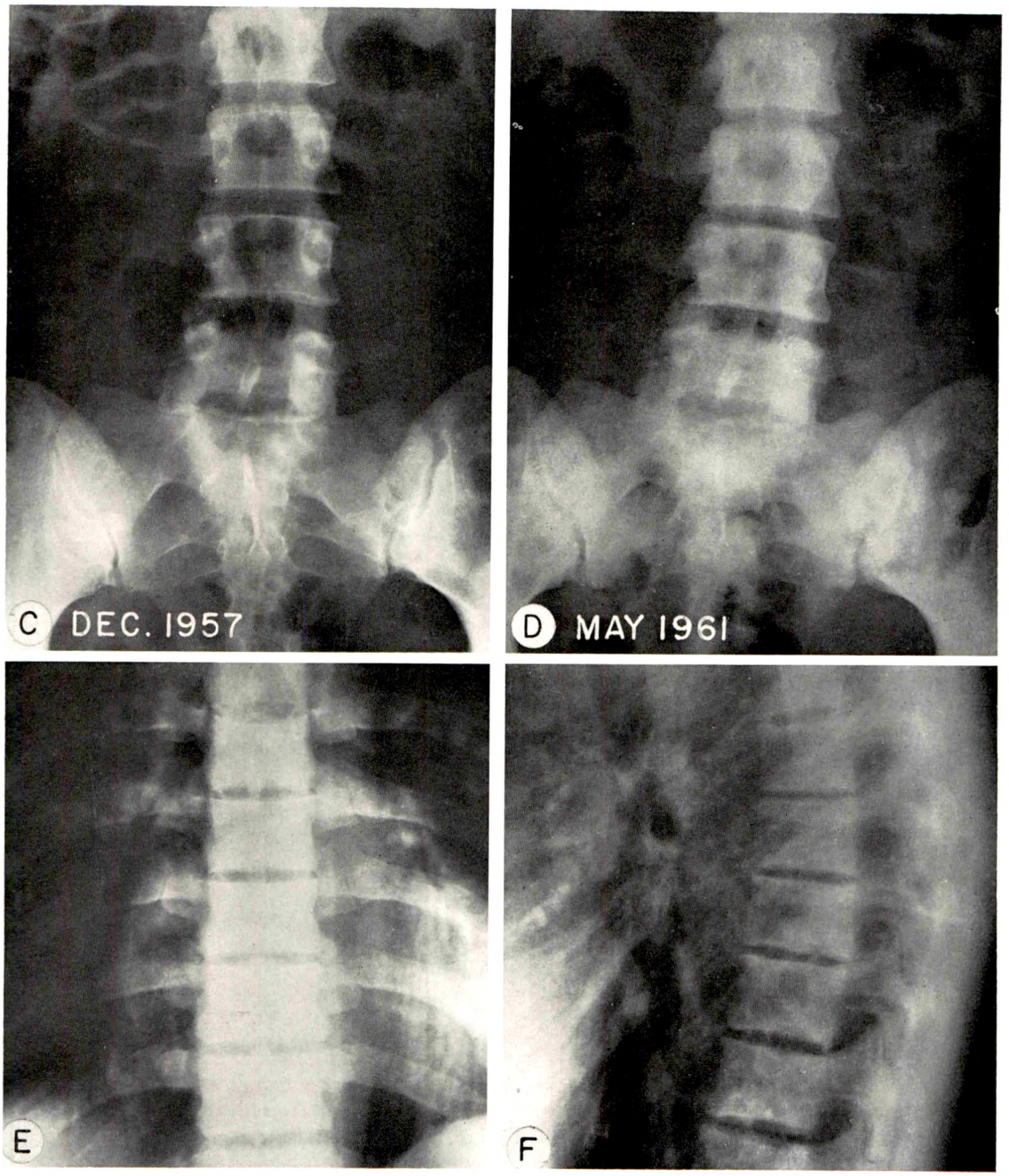


Fig. 3. Case III. (*C* and *D*) Although the roentgenogram made in December, 1957 (*C*) suggests normal skeletal structures, a study in May, 1961 demonstrates considerable sclerosis of the lumbar vertebrae. (*E* and *F*) The thoracic vertebrae are similarly involved. Thickest bone is noted in the periarticular zones of the bodies. Increased density of the ribs was evident on the original roentgenograms.

Fatigue recurred soon after discharge. The patient reported lethargy alternating with periods of nervousness and irritability. Vague back pain and occasional shortness of breath were also described. Transfusions of two units of blood were required at 2 month intervals to maintain the hematocrit in the range of 25 to 30 per cent. Other measures included orally administered sodium bicarbonate and Shohl's solution, and a low-protein diet.

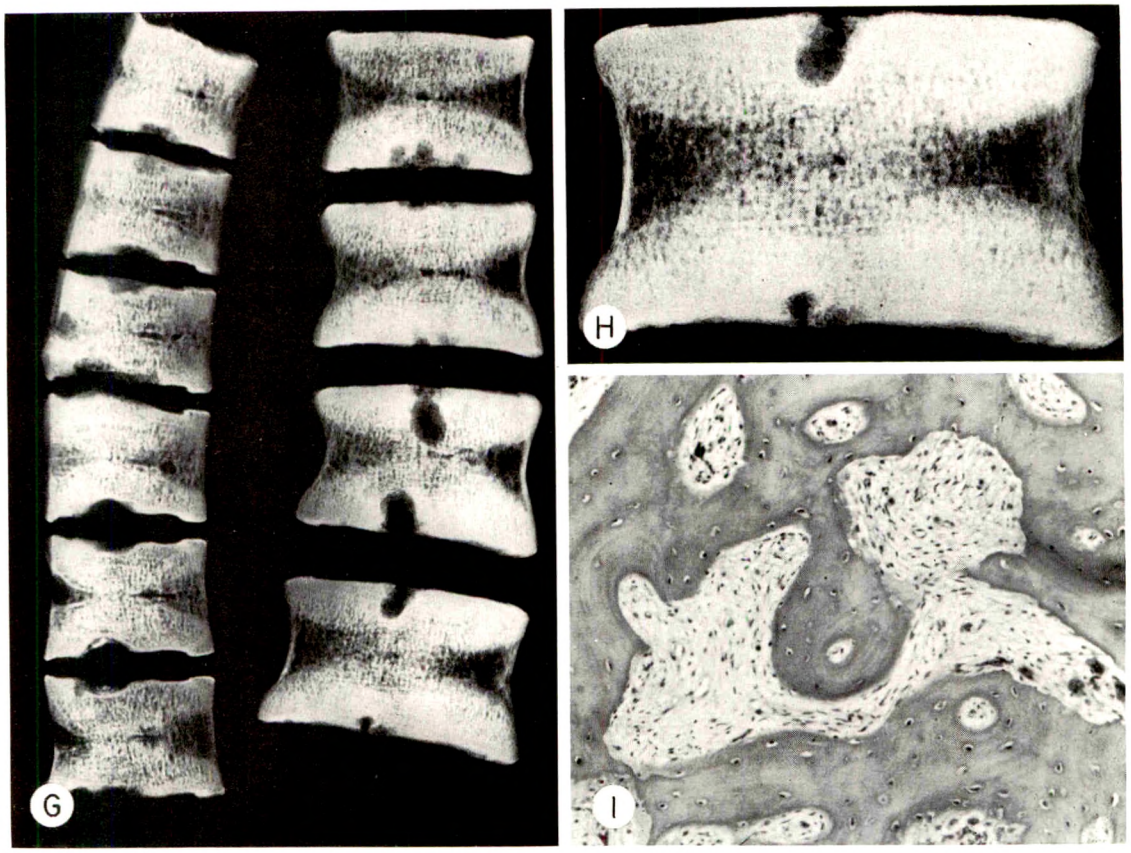


Fig. 3. Case III. (*G*) "Rugger-jersey spine." A roentgenogram of thin coronal and sagittal slabs of vertebrae obtained at autopsy demonstrates the concentration of dense bone about the end plates. Schmorl's nodes are present. (*H*) A photographic enlargement of a lumbar body from *G* emphasizes the increase in width and number of trabeculae which is responsible for the heightened bone density. (*I*) A photomicrograph from a dense area of the body shown in *H* reveals a thickened trabecular network, with associated foci of fibrous replacement of marrow. Multinucleated osteoclasts are seen, and trabeculae exhibit "scalloped" margins due to resorption (magnification, 110 ×). Similar examination of the central radiolucent zone in *H* did not show osteoporosis, but rather a fewer number of yet slightly widened trabeculae with abundant intervening normal marrow spaces.

In November, 1961, the patient was readmitted because of dyspnea, left pleuritic pain, and vomiting. A roentgenogram of the chest revealed pulmonary congestion and bilateral pleural effusions. Several rib fractures that had apparently occurred spontaneously also were noted. Congestive failure responded to bed rest, salt restriction, and digitalization, and she was discharged 21 days after admission. Blood urea nitrogen, nevertheless, rose progressively to 205 mg. per 100 cc. during this period.

In the following months, the patient's cardiorenal status steadily deteriorated. Dyspnea, ankle edema, and epistaxis became increasingly troublesome. The patient also reported dull nonradiating backache and hip discomfort. She was admitted for terminal care in May, 1962. Her condition was characterized by intermittent coma, frequent seizures, and extensive cutaneous and gastrointestinal bleeding. She died in June, 1962, at the age of 39 years.

An autopsy revealed pale scarred kidneys. Histologic examination confirmed chronic pyelonephritis. Specimens of thoracic and lumbar vertebrae (Fig. 3, *G* and *H*), rib, and clavicle demonstrated gross thickening, with increase in number and size of trabeculae evident microscopically. Figure 3*I* is a photomicrograph of a portion of a lumbar body. The calvarium, although also thickened, was predominantly porotic and was unusually soft. It could be cut

with scissors. Four uniformly hyperplastic parathyroid glands together weighed more than 2 gm. (average total weight, 120 mg.). These were composed largely of normal-sized chief cells.

Case iv. N.N., S.M.H. Unit Number 52-42-36. The patient, a 50 year old Negro woman, presented with a 30 year history of recurrent kidney infections. These began 2 years following delivery of her second child, when urinary "gravel" was found. Hematuria was first experienced in 1944. In 1948, a traumatic rupture of the right kidney required drainage. Also, in 1948, a left renal calculus was removed. The following year, a right perinephric abscess was drained.

A roentgenogram made in 1949 revealed a large right-sided branched calculus, as well as several smaller stones. A retrograde pyelogram demonstrated moderate dilatation of the right upper collecting elements, with more marked hydronephrosis on the left. The skeletal structures visualized appeared normal. Excretion of phenolsulfonphthalein from the right kidney approximated 5 per cent in 15 minutes, and there was only a trace from the left.

Between 1951 and 1961, the patient was admitted to other hospitals 16 times for acute pyelonephritis. Seven of these admissions occurred since July, 1959. Cultures of urine constantly yielded *E. coli*. Sulfonamides and chloramphenicol generally succeeded in controlling the acute episodes. Nitrogen retention rose steadily. Bone marrow studies, undertaken because of anemia, revealed hyperplasia consistent with chronic infection. Blood pressure remained normotensive.

In October, 1961, blood urea nitrogen was 111 mg. per 100 cc. A radiorenogram revealed no left kidney function, with little concentration and delayed excretion on the right. Roentgenograms (Fig. 4, *A–F*) demonstrated three large branched calculi on the right. Osteosclerosis of thoracic and lumbar vertebrae, first observed in 1958, had increased considerably. Roentgenograms of the hands revealed slight, but definite, subperiosteal resorption about the middle phalanges of several fingers. The lamina dura was virtually nonexistent.

Because of the increasing frequency of exacerbations and the rising nitrogen retention, relief of urinary obstruction was considered essential. The patient was referred to Strong Memorial Hospital, and in November, 1961, a right pyelotomy was performed. A greatly dilated renal pelvis, containing foul-smelling urine, was surrounded by extremely thin

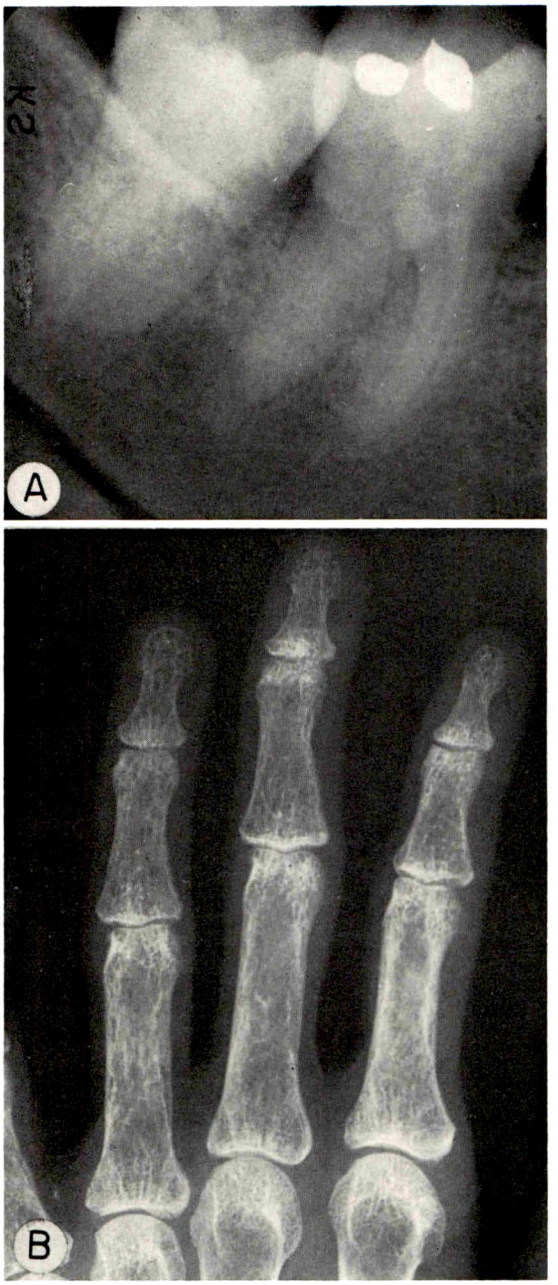


Fig. 4. Case iv. (*A*) A dental roentgenogram reveals absence of the lamina dura. (*B*) Lacy resorption of subperiosteal bone along the lateral borders of the middle phalanges is not as clearly shown as in Cases i, ii and iii, but is, nevertheless, sufficient for the diagnosis of hyperparathyroidism.

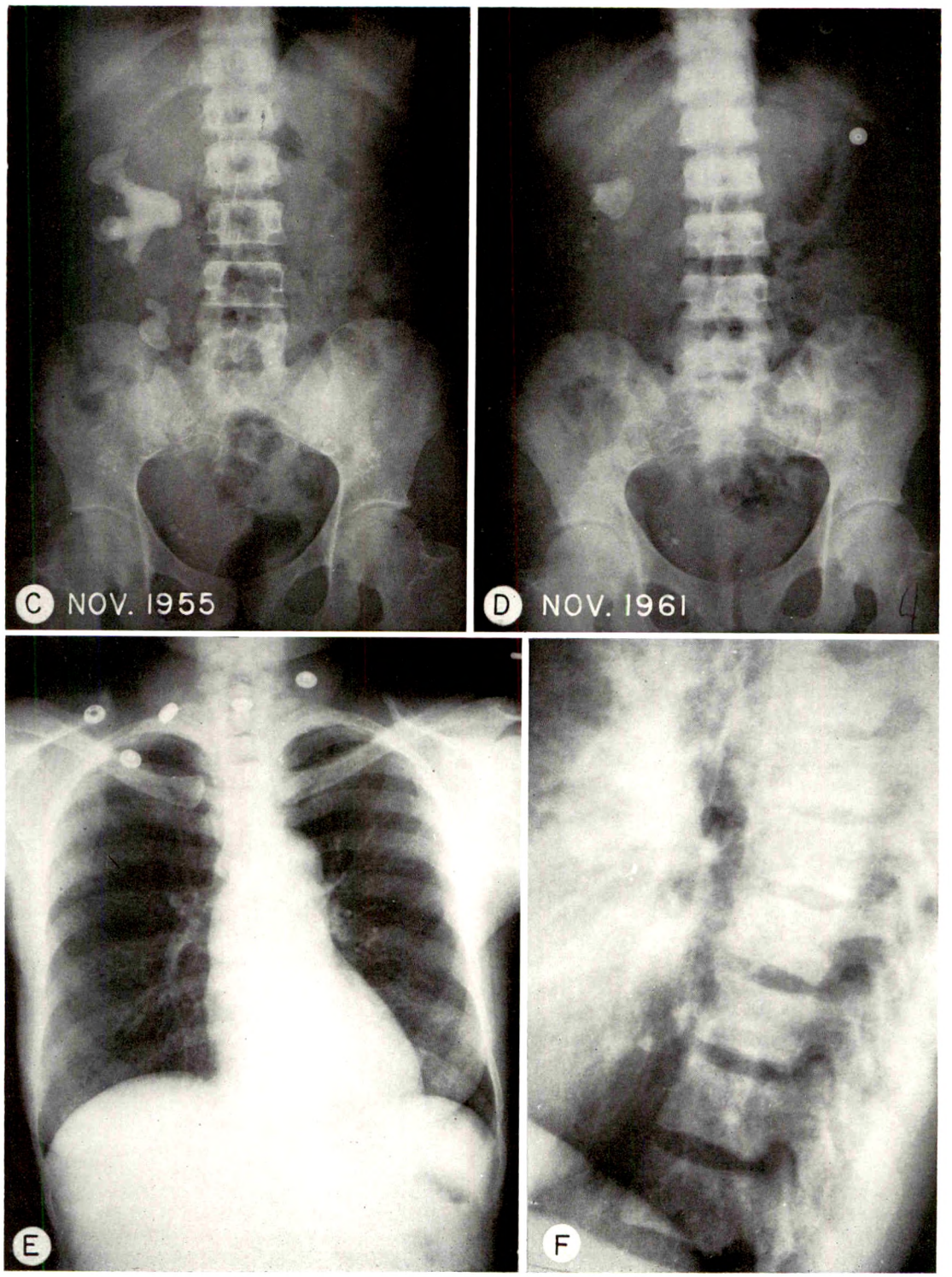


Fig. 4. Case IV. Normal bone density evident on a roentgenogram of November, 1955 (*C*) contrasts with osteosclerosis of the lumbar vertebrae, pelvis, and hips shown on an examination of November, 1961 (*D*). One renal calculus could not be removed at operation. (*E* and *F*) Ribs and thoracic vertebrae are also thickened.

parenchyma. Two large calculi were removed. One smaller stone shown on roentgenograms could not be located at operation. A biopsy of the kidney was interpreted as showing chronic pyelonephritis.

The convalescence was uneventful, and a significant decrease in nitrogen retention was observed. Well-being was, nevertheless, short-lived, and two re-admissions have since been required because of the recurrence of acute infection, accompanied by acidosis. The blood urea nitrogen has returned to the previous high values.

The biochemical findings for these 4 cases are summarized in Table I.

REVIEW OF THE LITERATURE

Prior to 1953, reports of osteosclerosis associated with renal disease were sparse. Ginzler and Jaffe,[10] in 1941, noted grossly detectable bone proliferation in 3 patients with chronic renal insufficiency. Microscopic evidence of increased osteoblastic activity was also observed in several other uremic patients. These authors also mentioned similar findings by Rutishauser and co-workers[16,17] in 1935 and 1936. In what is believed to be the only description to date in the American radiologic literature, Davis,[8] in 1953, reported osteosclerosis of the lumbar vertebrae, pelvis, and upper femora in an elderly patient with chronic pyelonephritis. Claireaux[4] in the same year described an 8 year old girl who, in the terminal stage of chronic glomerulonephritis, exhibited fusiform thickening of metacarpals and ribs. Cohen and Diamond,[5] also in 1953, related the unusual case of a 21

TABLE I

SUMMARIZED BIOCHEMICAL DATA

Date	BUN mg.%	Hct %	Hb gm.%	Ca mg.%	P mg.%	Alk. P'tase B.U.	CO_2 mEq./L.	K mEq./L.	Creatinine mg.%	A/G gm.%
					Case I					
May, 1953	73	17	—	7.0	5.6	29.4	—	—	10.2	4.4/3.4
Sept., 1953	89	—	3.5	6.6	5.9	—	10.4	4.9	—	—
Dec., 1953	155	21	—	2.4	11.1	24.0	3.0	5.7	—	3.3/4.6
					Case II					
Dec., 1948	61	—	10.5	—	—	—	—	—	1.1	—
Nov., 1952	88	—	10.2	—	—	—	—	—	4.5	—
Feb., 1954	92	—	8.1	—	—	—	—	—	5.5	—
June, 1957	75	23	8.6	9.5	8.0	21.0	12.0	5.1	13.1	3.5/1.6
Sept., 1957	110	18	5.3	10.6	7.3	28.0	14.1	5.6	14.0	—
					Case III					
Oct., 1954	43	—	8.5	—	—	—	—	—	—	—
Dec., 1959	87	21	—	—	5.7	—	—	—	7.4	—
April, 1960	127	30	—	—	—	—	—	—	—	—
May, 1961	154	21	—	10.1	6.5	30.2	16.0	5.1	11.4	3.8/3.0
Nov., 1961	205	23	—	10.5	6.4	30.6	19.0	5.6	16.5	3.4/2.7
May, 1962	230	19	—	10.5	11.6	27.3	21.0	5.4	26.5	2.9/2.3
					Case IV					
May, 1949	17	—	8.7	9.7	3.8	—	—	—	—	3.3/3.9
Nov., 1955	85	31	—	6.9	9.4	3.9	—	4.6	—	—
Jan., 1959	91	—	—	7.2	5.3	6.8	23.0	4.3	6.3	—
Oct.-Nov., 1961	116–161	21	—	8.8	5.2	12.9	22.0	5.8	5.5	3.4/3.6

Case III. Nov., 1961—24 hour urinary calcium excretion, 70 mg./L.
Case IV. Dec., 1960—24 hour urinary calcium excretion, 40 mg./L.

year old man with chronic pyelonephritis who developed proliferation of facial bones resembling leontiasis ossea. Other pathologic findings included slipped humeral and femoral epiphyses, coarctation of the aorta, and a functioning granulosa cell tumor of the testis. Subsequently, Crawford *et al.*[6] reported 3 cases of osteosclerosis associated with advanced renal insufficiency. Two of these patients presented signs of hypogonadism. One of the latter demonstrated roentgenographic findings of hyperparathyroidism. Brookfield *et al.*[3] added 2 cases of renal osteosclerosis, of which one exhibited typical bone and soft tissue stigmata of hyperparathyroidism. The patient presented by Karani[13] likewise demonstrated subperiosteal resorption and cystic changes coexisting with bony proliferation involving the skull, facial bones, and thoracolumbar vertebrae. Wolf and Denko[21] described 7 cases of osteosclerosis associated with chronic renal disease. One was characterized by striking hyperostosis of the frontal bone and base of the skull. There was no mention of hyperparathyroidism. Kaye *et al.*,[14] in an excellent study of bone and biochemical changes in renal disease, described 12 more cases of osteosclerosis. Five demonstrated roentgen signs of secondary hyperparathyroidism, and 4 of these were reported as having microscopic evidence of osteomalacia. Finally, Cronqvist,[7] in 1961, reviewing "osteonephropathy," reported 7 additional cases of generalized osteosclerosis. In 5, hyperparathyroidism was present.

In the foregoing cases of osteosclerosis, changes of hyperparathyroidism were believed to have been secondary to renal disease. However, 5 cases of proliferation of bone in primary hyperparathyroidism have been reported. Beveridge *et al.*,[2] in 1959, described a 63 year old woman who had recurrent urinary calculi for 22 years and signs of progressive renal failure for 6 years. Roentgenograms revealed bony thickening of the skull, vertebral column, pelvis, femora, tibiae, and fibulae, as well as the resorptive changes of hyperparathyroidism. Hypercalcemia suggested primary hyperparathyroidism, and, although the patient declined surgery, autopsy confirmed a swelling of the neck to be a parathyroid adenoma.

Ellis and Hochstim,[9] in 1960, described focal areas of sclerosis in the skulls of 5 patients with primary hyperparathyroidism. Three cases were reported in some detail. None were afflicted with renal insufficiency, although 2 presented a history of calculi. In one, scattered areas of new-bone formation were demonstrated in the lumbar vertebrae, pelvis, and femora, as well as the skull. Adenomas were found in all.

Wills *et al.*[20] reported the case of a 63 year old woman with renal insufficiency who demonstrated osteosclerosis of the skull, ribs, and thoracolumbar vertebrae, in addition to subperiosteal resorption of phalanges and cyst formation. At surgery, a calcified cervical mass was found to be an unusually large hemorrhagic parathyroid adenoma. Postoperatively, the bony resorptive changes regressed, although the osteosclerosis persisted.

These 5 cases of primary hyperparathyroidism appear to disprove an earlier opinion of Brookfield *et al.*[3] that bony sclerosis invariably signified that hyperparathyroidism when present was always secondary to renal disease.

As shown in Table II, chronic pyelonephritis has been reported to be the most common renal disease associated with osteosclerosis. Kaye *et al.*[14] suggest that the relative infrequency of osteosclerosis in other diseases of the kidney may result from the need for a sufficiently long compensated illness. As would be expected, the laboratory values usually have revealed nitrogen retention, hyperphosphatemia, hypocalcemia, and an elevated serum alkaline phosphatase. Also, a severe anemia has been present in most cases. Exceptions, however, have occurred. Thus, in Case 9 of Kaye and co-workers,[14] osteosclerosis of the vertebral column and femora was present 5 years before the patient succumbed to renal failure and at a time when the blood urea

TABLE II

SUMMARY OF REPORTED CASES

Author	Case No.	Age	Sex	Disease	Bones Involved	Associated Hyperparathyroidism	Remarks
1. Davis[8] (1953)	1	68	M	Chronic pyelonephritis	vertebrae, pelvis, femora	o	
2. Claireaux[4] (1953)	1	5	F	Chronic glomerulonephritis	skull (base), ribs, hands	o	also, pulmonary tuberculosis
3. Cohen and Diamond[5] (1953)	1	17	M	Chronic pyelonephritis secondary to congenital obstruction	skull, face, vertebrae, ribs, pelvis	+	face resembled leontiasis ossea; also, slipped epiphyses, coarctation of aorta, and granulosa cell tumor of testis
4. Crawford *et al.*[6] (1954)	1	42	M	Chronic pyelonephritis	skull (base), ribs, pelvis, long bones, hands	o	backache
5. Crawford *et al.*[6] (1954)	2	17	F	Chronic pyelonephritis	vertebrae (R-J)	o	hypogonadism; disproportionate length of limbs
6. Crawford *et al.*[6] (1954)	3	26	M	Chronic pyelonephritis secondary to neurogenic bladder	vertebrae (R-J)	+	hypogonadism; disproportionate length of limbs
7. Brookfield *et al.*[3] (1955)	1	26	M	Chronic pyelonephritis	vertebrae (R-J)	+	hypogonadism
8. Brookfield *et al.*[3] (1955)	2	47	M	Chronic pyelonephritis	skull, vertebrae, tibiae	o	
9. Karani[13] (1955)	1	41	F	Chronic pyelonephritis	skull, vertebrae (R-J)	+	
10. Wolf and Denko[21] (1958)	1	42	F	Chronic glomerulonephritis	skull, vertebrae, ribs, sternum, pelvis, femora	o	
11. Wolf and Denko[21] (1958)	2	58	M	Chronic pyelonephritis	vertebrae, sacrum	o	backache; minimal deafness
12. Wolf and Denko[21] (1958)	3	55	M	Chronic pyelonephritis	vertebrae, sacrum, ribs, right tibia and fibula	o	backache
13. Wolf and Denko[21] (1958)	4	64	M	Chronic pyelonephritis	vertebrae	o	minimal deafness; also, diabetes
14. Wolf and Denko[21] (1958)	5	53	M	Chronic glomerulonephritis	vertebrae, ribs, pelvis	o	minimal deafness; (back pain attributed to herniated disk)
15. Wolf and Denko[21] (1958)	6	62	M	Chronic glomerulonephritis	vertebrae, pelvis	o	backache
16. Wolf and Denko[21] (1958)	7	21	F	Chronic pyelonephritis secondary to neurogenic bladder	vertebrae, ribs, pelvis	o	
17. Beveridge *et al.*[2] (1959)	1	63	F	Primary hyperparathyroidism	skull, vertebrae (R-J), femora, tibiae	+	adenoma confirmed at autopsy; also, colloid goiter; past nephrectomy for calculi

(R-J) = "Rugger-jersey spine." (Dent)

(TABLE II *continued on pages 1164–1165*)

TABLE II (*Continued*)

Author	Case No.	Age	Sex	Disease	Bones Involved	Associated Hyperparathyroidism	Remarks
18. Ellis and Hochstim[*9] (1960)	1	27	M	Primary hyperparathyroidism	skull	+	adenoma confirmed surgically; also, papillary carcinoma of thyroid; renal calculi
19. Ellis and Hochstim[9] (1960)	2	42	F	Primary hyperparathyroidism	skull	+	sclerosis originally limited to margins of resorptive lesions; adenoma confirmed surgically; history of renal calculi
20. Ellis and Hochstim[9] (1960)	3	46	F	Primary hyperparathyroidism	skull, vertebrae, pelvis, femora	+	adenoma confirmed surgically; also, nontoxic nodular goiter
21. Kaye *et al.*[14] (1960)	1	32	F	Chronic pyelonephritis	skull, mandible, vertebrae (R-J), ribs, clavicles, femora, hands	+	
22. Kaye *et al.*[14] (1960)	2	22	M	Chronic pyelonephritis	skull, face, vertebrae, ribs, clavicles, pelvis, femora, tibiae, hands	+	moron; chronic lead intoxication in childhood
23. Kaye *et al.*[14] (1960)	3	26	M	Chronic pyelonephritis	vertebrae, pelvis	+	
24. Kaye *et al.*[14] (1960)	4	16	F	Chronic pyelonephritis secondary to ureteral stricture	vertebrae, pelvis, femora, tibiae, radii, ulnae, hands	+	hypogonadism; genu valgum, with tenderness about knees
25. Kaye *et al.*[14] (1960)	5	47	M	Chronic pyelonephritis	vertebrae (R-J), clavicles, pelvis, knees, elbows, hands, feet	+	also, gouty arthritis
26. Kaye *et al.*[14] (1960)	6	15	M	Chronic pyelonephritis	vertebrae, pelvis, femora	o	also, osteomalacia
27. Kaye *et al.*[14] (1960)	7	63	M	Chronic pyelonephritis with nephrosclerosis	vertebrae (R-J), ribs, femora, tibiae, fibulae	o	also, osteomalacia
28. Kaye *et al.*[14] (1960)	8	35	M	Chronic pyelonephritis	vertebrae, ribs, clavicles, femora	o	also, osteomalacia
29. Kaye *et al.*[14] (1960)	9	77	M	Chronic pyelonephritis	skull, vertebrae, sternum, pelvis, femora, feet	o	also, osteomalacia
30. Kaye *et al.*[14] (1960)	10	59	M	Chronic pyelonephritis	vertebrae	o	also, diabetes
31. Kaye *et al.*[14] (1960)	11	18	F	Chronic pyelonephritis	skull, vertebrae, ribs, femora	o	
32. Kaye *et al.*[14] (1960)	12	53	M	Chronic pyelonephritis	skull, vertebrae, ribs, sternum, pelvis, hands, feet	o	also, gouty arthritis
33. Wills *et al.*[20] (1961)	1	63	F	Primary hyperparathyroidism	vertebrae (R-J)	+	adenoma confirmed surgically

* Ellis and Hochstim[9] mention 2 additional patients with primary hyperparathyroidism and sclerotic foci in the calvarium, but do not report sufficient details to permit tabulation.

Table II (*Continued*)

Author	Case No.	Age	Sex	Disease	Bones Involved	Associated Hyperparathyroidism	Remarks
34. Cronqvist[7] (1961)	1	17	M	Polycystic disease	entire skeleton	+	bone pain
35. Cronqvist[7] (1961)	2	36	F	Chronic pyelonephritis with horseshoe kidney	vertebrae	+	joint pain
36. Cronqvist[7] (1961)	3	54	F	Chronic pyelonephritis	vertebrae (R-J), other parts	o	joint pain
37. Cronqvist[7] (1961)	4	25	M	Nephrosclerosis	vertebrae, sternum, pelvis, femora, tibiae	+	
38. Cronqvist[7] (1961)	5	37	F	Chronic pyelonephritis	vertebrae, pelvis	+	back and leg pain
39. Cronqvist[7] (1961)	6	29	M	Chronic pyelonephritis	generalized	+	
40. Cronqvist[7] (1961)	7	48	M	Chronic glomerulonephritis	vertebrae	o	backache and generalized joint pain
41. Zimmerman (1962)	1	53	F	Chronic pyelonephritis	vertebrae (R-J), ribs, pelvis, femora	+	
42. Zimmerman (1962)	2	21	M	Chronic pyelonephritis secondary to congenital obstruction	skull, vertebrae (R-J)	+	
43. Zimmerman (1962)	3	39	F	Chronic pyelonephritis	vertebrae (R-J), ribs, pelvis	+	back and hip pain
44. Zimmerman (1962)	4	50	F	Chronic pyelonephritis	vertebrae (R-J)	+	renal calculi

nitrogen measured a modest 25 mg. per 100 cc. Also, significant osteosclerosis was observed in Wolf and Denko's[21] Case 3 and in Case 3 of Ellis and Hochstim,[9] although the blood urea nitrogen of each was recorded as 31 mg. per 100 cc. and 9 mg. per 100 cc., respectively. In addition, Cases 3 to 6 in Wolf and Denko's series were not anemic.

In 23 of the 44 tabulated cases of osteosclerosis, bone changes of hyperparathyroidism have been present. As noted, 5 of these are believed to have represented primary hyperparathyroidism, with confirmation of an adenoma in each. Other cases, at autopsy, usually have exhibited hyperplasia of parathyroid glands.

Histologic examination of sclerotic bone in these cases has revealed trabeculae of cancellous bone to be increased in width and number, and arranged in a greatly thickened continuous network (Fig. 1*D* and 3*I*). Associated foci of osteoclastic activity have been commonly seen, with coexisting areas of fibrous replacement of trabeculae. As mentioned earlier, 4 of the cases of Kaye *et al.* likewise presented the microscopic finding of widened osteoid seams indicative of osteomalacia.

The reported incidence of skeletal discomfort has varied. Although only one of 12 patients in Kaye and co-workers' group experienced local tenderness, 3 of 7 patients in Wolf and Denko's series and 5 of Cronqvist's 7 patients were described as having bone and joint symptoms. Cronqvist[7] added that these complaints "were the indication for roentgen examination in 4 cases. In 3 the pain was dull, while in one it was stabing." In Case III currently

presented, the patient experienced a dull aching sensation in the low back and hips during her final 6 months of life.

It might also be noted that 3 of Wolf and Denko's patients were observed to have minimal deafness and that in Case 1 presently reported there was a conduction deficit in the right ear. The autopsy of the latter patient did not include a study of the auditory apparatus.

SUGGESTED MECHANISMS OF DEVELOPMENT

Although the association of secondary hyperparathyroidism and chronic renal disease has been well established, the mechanism of the bony resorption has not been fully explained. Why proliferation of bone should also occur occasionally is even less understood.

With respect to the resorptive process in secondary hyperparathyroidism, most explanations are primarily concerned with the base-conserving ability of the diseased kidney.[1,12,19] It is usually considered that ammonium production, hydrogen ion secretion, and bicarbonate resorption are impaired, and that fixed bases, including sodium and calcium salts, are utilized to promote the excretion of acid metabolites. Ensuing hyperphosphatemia, or perhaps the accompanying hypocalcemia, is then believed to stimulate the parathyroid glands to restore balance by release of osteoclastic hormone. Several investigators have considered the osseous changes to be a direct result of acidosis, with parathyroid hyperplasia as a secondary phenomenon.[10,12] A recent writer[19] has speculated on the role of acquired vitamin D resistance in the pathogenesis of the skeletal findings.

In hyperparathyroidism, it is also believed that some new bone formation may accompany the resorption of bone. It is not established, however, whether the production of bone results from an unidentified component of the parathyroid hormone, or represents a compensatory reaction to heightened stress that may be associated with resorption. Selye,[18] in 1932, and Jaffe,[12] in 1933, reported osteosclerosis in rats following prolonged injection of parathyroid extract. It has since been postulated that osteoclastic processes may partially subside leaving osteoblastic functioning predominant.[3,6] The reasons are unknown, but may be related to remission of renal disease, with lessened acidosis or increased vitamin D sensitivity. More detailed understanding is lacking. One can speculate that the increasing number of reported cases of osteosclerosis may in part reflect the improved supportive therapy that has become available in the past 2 decades.

Regarding other theories, Crawford *et al.*[6] have noted that the involved bones are generally those most active in hematopoiesis, and have suggested that chronic anemia may be a leading factor in the production of osteosclerosis. They have likewise advanced the possibility that hypogonadism might in some manner be implicated. This condition has indeed been present in their Case 2 and Case 3, in Brookfield and co-workers'[3] Case 1, and in Case 4 of Kaye *et al.*[14] Also, the patient of Cohen and Diamond[5] was afflicted with an estrogen-producing testicular tumor. A relationship between osteosclerosis and pituitary-adrenal-gonadal dysfunction might thus exist. Finally, Ellis and Hochstim[9] have suggested that the bone proliferation in cases of primary hyperparathyroidism might result from healing accompanying such local changes as infarction or hemorrhage in the adenoma. As mentioned, the tumor resected in the case of Wills and his co-workers[20] was described as hemorrhagic.

ROENTGEN FINDINGS

Skeletal changes in hyperparathyroidism are well known.[15] Widespread cyst-like areas of resorption—classic osteitis fibrosa cystica—are rarely seen in secondary hyperparathyroidism, probably because of limited patient survival. Earlier bone changes, however, are identical in primary and secondary hyperparathyroidism. These include an unusual lacy erosion of subperiosteal bone, most pronounced about the radial margins of the middle phalanges; its

dental counterpart—resorption of periodontal membrane—causing loss of lamina dura; destruction of the outer ends of the clavicles; a distinctive granular "ground glass" appearance of the calvarium; and, finally, generalized osteoporosis. The confusion which may arise when osteosclerosis is observed instead of the expected osteoporosis has been mentioned earlier.

The initial finding in cases of osteosclerosis is an accentuation of the trabecular pattern. Coalescence of trabeculae and increase in bone density follow. In the later stages, architectural detail may be greatly obscured (Fig. 3, *D* and *E*).

The most common site of osteosclerosis has been the vertebral column, particularly the lower thoracic and upper lumbar regions. Cronqvist mentions involvement limited to a single vertebra. Usually vertebral bodies have been described as homogeneously sclerotic. Many authors, however, have noted that the thickening is most conspicuous in zones adjacent to the superior and inferior end plates, the intervening bone being apparently porous. The resulting horizontal striped appearance has inspired Dent's[13] graphic description, "rugger-jersey spine." The second and third currently reported cases (Fig. 2 *D*; and 3, *G* and *H*) well illustrate this finding. It is also demonstrated in Cases I and IV, but to a lesser degree. Actually, despite the roentgen appearance, microscopic examination of bone from the central lucent zone of a lumbar vertebra in Case III did not reveal osteoporosis, but rather a fewer number of yet slightly widened trabeculae, surrounding essentially normal marrow spaces. The reason for the distribution of sclerosis is not clearly understood, but may be related to greater vascularity of the periarticular regions. Hinkel and Beiler[11] have observed a similar "sandwich vertebra" in cases of adult osteopetrosis. In other reported cases, including the present Case IV, sclerosis alternated diffusely with rarefaction, producing a peculiar granular appearance (Fig. 4, *D*, *E* and *F*).

The next most frequently mentioned sites have been the pelvis, ribs, and skull (Table III). It should be realized, of course, that the extent of these roentgenographic examinations has varied greatly. Tubular bones have been less involved than flat bones. When the former are affected, the osteosclerosis is present more often in the proximal portions. Uncommon sites have been the face, sternum, and clavicles.

TABLE III

REPORTED SITES OF OSTEOSCLEROSIS

44 CASES

Site	No. of Cases
vertebrae	37
pelvis	18
ribs	16
skull	16
femora	12
tibiae	7
hands	7
sternum	4
clavicles	4
face	3
feet	3
others:	
"long bones"	7
"generalized"	3

DIFFERENTIAL DIAGNOSIS

In the presence of advanced renal insufficiency, differential diagnosis should offer no problem. It is nevertheless conceivable that renal osteosclerosis might be discovered incidentally, and that other causes of "white bones" may need to be excluded. Thus, in older men, acid phosphatase determinations are certainly indicated in evaluating possible metastatic carcinoma of the prostate. Differentiation from other types of osteoblastic secondary carcinoma, as well as the sclerotic variety of myeloma, could prove more troublesome, especially if renal osteosclerosis is associated with alternating rarefaction. Osteitis deformans (Paget's disease), with actual cortical and trabecular widening, should not present difficulty. Patients with myelofibrosis almost invariably exhibit spenomegaly. To

investigate the possibility of fluorosis, study of fluoride intake will be helpful. An unusual adult type of osteopetrosis may appear similar to renal osteosclerosis; however, this entity is typically discovered in childhood, and strong familial tendencies plus associated congenital anomalies are usually present. Hypoparathyroidism results in some decreased resorption and increased deposition of bone; nevertheless, if this is detectable at all roentgenographically, it is almost always slight, and basal ganglia calcification is a far more common roentgenographic manifestation.

SUMMARY

Four cases of osteosclerosis associated with advanced renal insufficiency have been presented. Bone changes of hyperparathyroidism, believed to be secondary, accompanied each. The literature concerning this apparently paradoxical combination of findings has been reviewed.

No satisfactory explanation for renal osteosclerosis is available. Osteoblastic activity may be caused by an as yet poorly understood independent component of parathyroid hormone, or may possibly represent a compensatory reaction to the stress of osteoclastic resorption. It has been suggested that bone proliferation may predominate following some decrease in osteoclastic function of parathyroid hormone, possibly because of remission of renal disease.

The site most commonly involved is the thoracolumbar portion of the vertebral column. A peculiar distribution of sclerosis about the end plates of the vertebral bodies is characteristic (rugger-jersey spine).

Awareness of this entity, clinical history, and serum chemistries should leave little doubt as to the correct differentiation from other causes of osteosclerosis.

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ADDENDUM

Since the acceptance of this paper for publication, osteosclerosis involving the lumbar vertebrae as well as several other sites has been reported in a case each of primary and secondary hyperparathyroidism. (Templeton, A. W., Jaconette, J. R., and Ormond, R. S. Localized osteosclerosis in hyperparathyroidism. *Radiology*, June, 1962, *78*, 955–958.)

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THE SUBTRACTION TECHNIQUE: EXPERIENCES WITH APPLICATION TO TRANSFEMORAL RENAL ARTERIOGRAPHY*

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THE subtraction technique, as a method of enhancing the radiographic visualization of contrast material casting a faint shadow, has been described and extensively discussed in the German and Dutch literature by Ziedses des Plantes.[3–7] The most recent of des Plantes' contributions is a very complete monograph on the subject[7] in which the theory behind the process of subtraction in radiography and its clinical applications are reported. These include application to cerebral angiography, pneumoencephalography, aortography, angiocardiography, myelography, ocular foreign body localization, and the study of the heart without the presence of added contrast material, *e.g.*, valvular calcification visualization.

The procedure of subtraction seemed so promising that we have been applying it to various kinds of serialographic contrast studies in an attempt to assess its usefulness as a routine radiographic procedure. This paper presents our initial experiences with the technique as applied to renal arteriography.

THEORY AND TECHNIQUE

The principle of subtraction in radiology is demonstrated with the following example. A transparent positive print (Fig. 1*B*) is made from an original roentgenogram (Fig. 1*A*) before the introduction of contrast material, and is superimposed upon a roentgenogram after injection of contrast material, with the patient and roentgen-ray tube in the identical position as in the original roentgenogram. (In Figure 1*C* the word "SUBTRACTION" represents the added contrast material). The resultant composite (Fig. 1*D*) suppresses all contrasting shadows which were present on both the original roentgenogram and the one made after the addition of contrast material, leaving the added contrast material as the prominent feature. The subtraction process may be enhanced further by then making a transparent positive of the composite (Fig. 1*E*).

The technique which we use for making the transparent positive films consists of exposing Kodak Blue Brand film, overlaid with the film to be contact printed, to incandescent light. The exposure to light is made with the films in a cassette, the intensifying screens of which have been removed and the front face replaced with ordinary glass. The light source used is a small bulb (15 watts) which is kept at a minimum distance of 6 feet from the film. The actual exposure time is so dependent upon the light-film distance, the density of the film being contact printed, and the processing technique that no standard exposure times can be given. Proper exposure times can best be determined for a given set of conditions by trial and error. Once a given system of exposure is used, it is quite easy to judge the exposure time and distance necessary and the procedure is then simple to perform. We have found it valuable to make several positive transparent prints routinely, each of a different density, for each film being printed. This is done because the density on the original film generally varies between such extremes that no single print can satisfactorily subjugate all of the densities present. For this reason, as pointed out by des Plantes,[7] films exposed originally with high kilovoltage roentgen-

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ray techniques are easier to work with since they are of a more uniform over-all density. All films are processed in a Kodak X-omat unit.

In an effort to make the method adaptable to the usual radiologic department, we have kept the procedure as simple as possible by employing the roentgenographic exposures and processing techniques in daily use in this department. The only additional equipment is a cassette with a glass front. While not essential, it is convenient to have a horizontally positioned view box with a variable rheostat so that compositions of varying densities may be easily superimposed and studied.

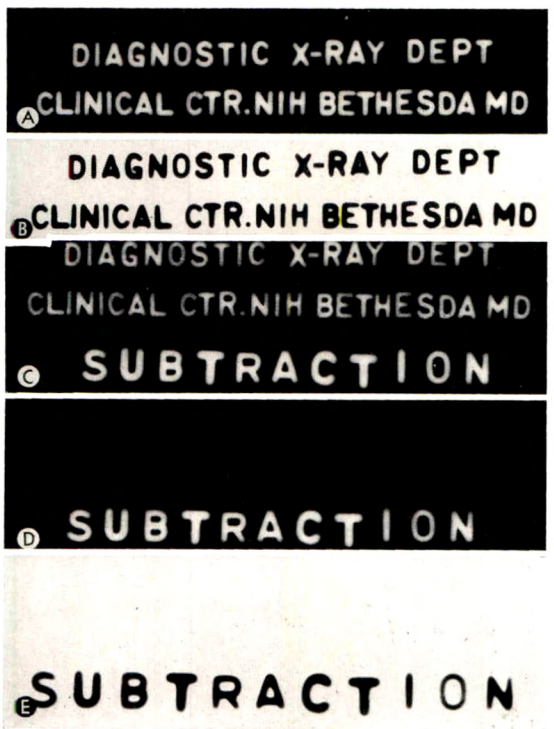


Fig. 1. The principle of subtraction in radiography. (*A*) The original roentgenogram, which can be considered as the survey film for a serialographic study. (*B*) The positive transparent print made from the original roentgenogram. (*C*) A roentgenogram made after the addition of a word to the object roentgenographed in *A*. The word "SUBTRACTION" can represent added contrast material in a serialographic study. (*D*) The composite picture obtained from superimposing the print shown in *B* and the film made after the addition of contrast material *C*, demonstrating the suppression of all shadows except for the added contrast material, "SUBTRACTION." (*E*) The positive print of the composite shown in *D*, demonstrating enhancement of the subtraction process.

DISCUSSION

The requirements for the use of the subtraction technique include:

1. A roentgenogram must be available without contrast material in the vessels of interest, from which the transparent positive contact print can be made. A roentgenogram in the capillary or venous phase can be used just as well as a scout roentgenogram to study the arterial phase. This is convenient since frequently some motion of the patient takes place between the time a scout roentgenogram is made and the actual serialographic run. An extrapolation of this concept is that, for teaching purposes, one may superimpose a print of the arterial phase over the original of the venous phase of a serialographic study and then make a print of the composite. This will show both vascular phases on one film with the bony shadows suppressed.[7]

2. No motion of the patient or roentgen-ray tube can take place between the time of the exposure of the film from which the positive print is to be made and the exposure of the film for study. This requirement makes obvious the fact that the subtraction technique finds its most convenient application in serialographic contrast examinations (*e.g.* renal arteriography, cerebral angiography and femoral arteriography). Des Plantes did make attempts to apply the technique to pneumoencephalography by duplicating the position of the patient in films exposed before and after the injection of the air with some success.[5,7]

USE IN RENAL ARTERIOGRAPHY

We perform renal arteriography by employing the Seldinger method of percutaneous transfemoral catheterization.[1] Approximately 20 cc. of 50 per cent hypaque is injected with a Gidlund power syringe at 10 kg./cm.^{2} of pressure. This technique generally supplies good visualization of the renal

arteries in their entirety. However, in an occasional patient, only faint opacification of a renal artery is obtained due to overlying bone shadows, to obesity of the patient, or to a combination of these factors. In these instances the subtraction technique appears to be of definite value.

We found that no diagnoses were made by the subtraction technique which were not already made from the original roentgenograms, but the outlines of several renal arteries, portions of which were obscured on the original studies, appeared clearer. This is illustrated in Figures 2 and 3. In Figure 2*C*, the right renal artery's lower margin is lost in the bone shadows overlying it, although the vessel is interpreted as being probably normal. After subtraction of the

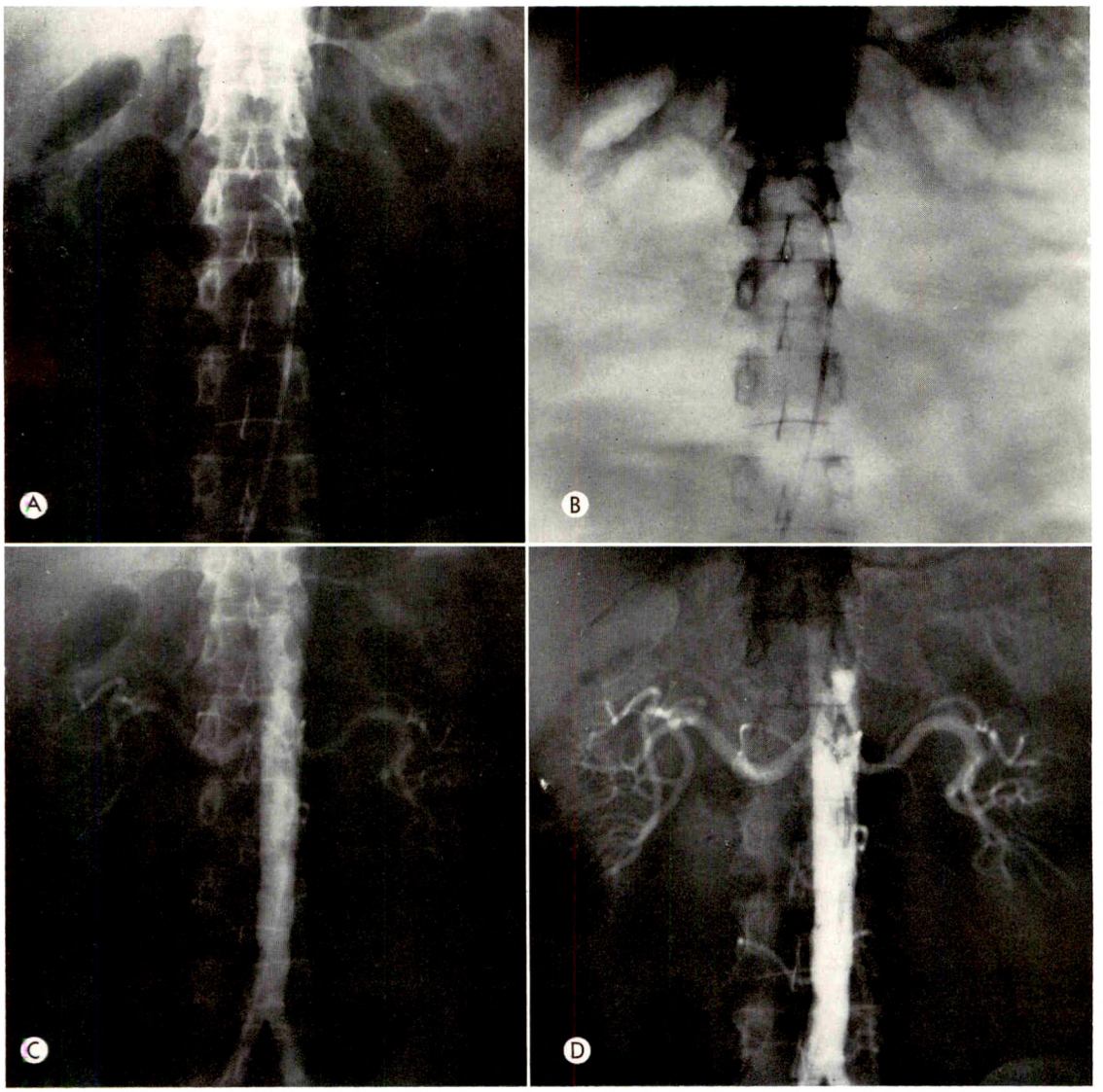


FIG. 2. (*A*) The survey film from a renal arteriogram. (*B*) The positive transparent contact print of the survey film. (*C*) A film from the serialographic renal arteriogram showing only faint visualization of the right renal artery. (*D*) The composite film obtained from superimposing the transparent print shown in *B* and the film from the serialographic run shown in *C*, demonstrating good visualization of the right renal artery.

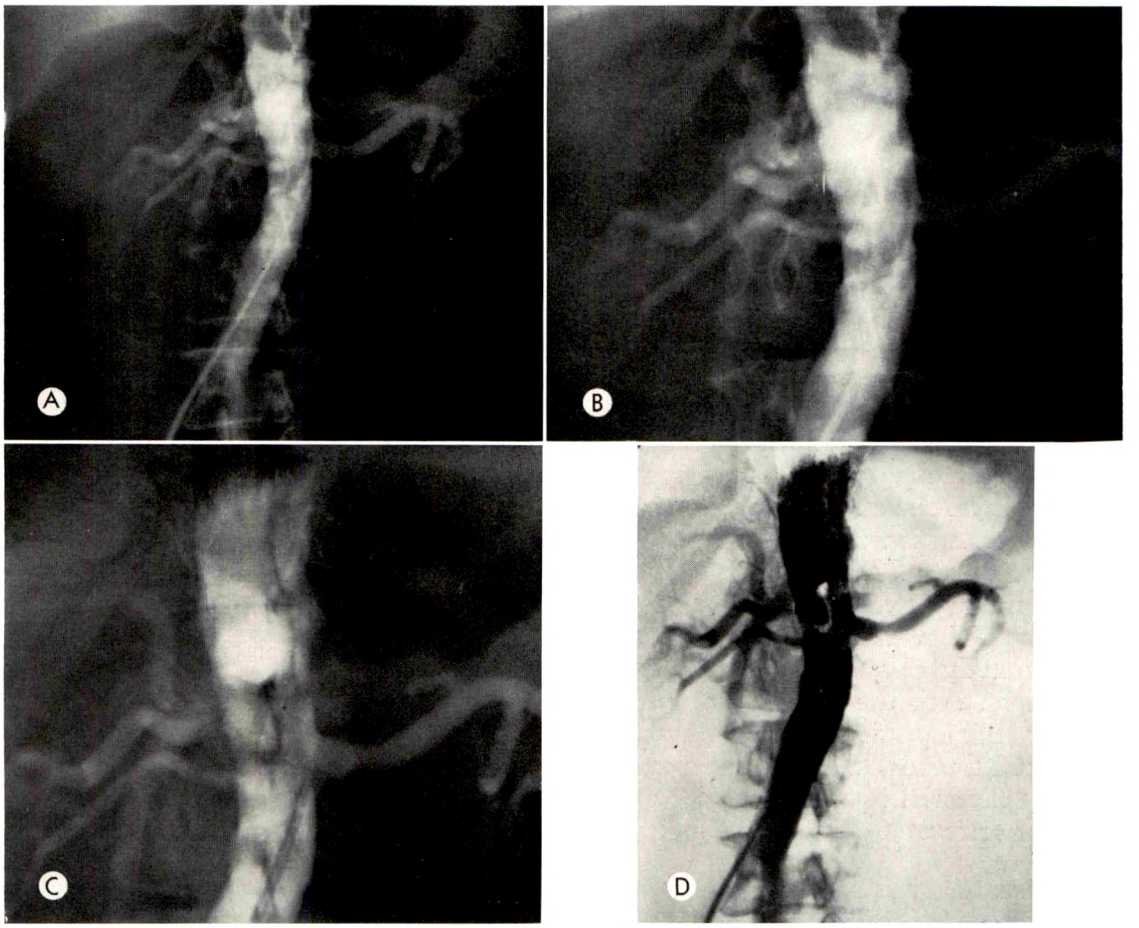


Fig. 3. (*A*) A renal arteriogram showing the proximal portion of the superior right renal artery to be incompletely visualized. (*B*) An enlargement of the renal arteries shown in *A*. (*C*) The composite film obtained by using the subtraction technique. Note that the bone shadows have been suppressed and the proximal portion of the superior right renal artery is seen better, but still faintly. (*D*) The print of the composite film shown in *C*, demonstrating better delineation of the superior right renal artery, the appearance of which is normal.

confusing shadows (Fig. 2*D*), both renal arteries are more clearly seen and it can be stated with certainty that they are normal. It should be noted that the bone shadows are suppressed mainly in the region of the renal arteries. This demonstrates the fact that a positive transparency of a density which is proper to subtract the bone shadows in one region frequently will not afford subtraction in other regions.

In Figure 3, *A* and *B* the outlines of the proximal portion of the superior right renal artery are questionable. After subtraction (Fig. 3*C*), this portion of the artery is visualized more clearly, but its outlines are still faint. The value of contact printing the subtraction composite is shown in Figure 3*D* where the portion of the superior right renal artery in question is seen clearly and appears to be normal. This patient had an exploratory laparotomy and the renal arteries were found to be normal.

We do not usually perform intravenous renal arteriography as described by Steinberg.[2] The contrast material reaching the renal arteries in this method would, of necessity, be less concentrated than with the transfemoral catheterization technique. Institutions utilizing the intravenous method might therefore find the subtrac-

tion technique a real aid in visualizing the renal arteries. Since any technique of renal arteriography may occasionally result in poor visualization of the renal arteries because of overlying shadows, the application of the subtraction technique might make a repeat examination of the patient unnecessary.

In addition to its use in renal arteriography, we are investigating the clinical value of subtraction in angiocardiography. We also plan to use subtraction in an effort to make intravenous pan-cerebral angiography a more useful procedure. One of the major objections to this procedure appears to be the faintness of the intravenously injected contrast material relative to the bone density.

We further intend to investigate the use of subtraction to improve the roentgenographic study of the vessels in the neck when done with the intravenous method. This would be particularly useful since one is reluctant to do a direct puncture and contrast material injection into a possibly occluded artery.

SUMMARY AND CONCLUSIONS

The subtraction technique is being applied to various serialographic contrast studies in an attempt to evaluate its usefulness. The method being used is described and its application to renal arteriography is discussed. It is concluded that the technique of subtraction is of value in defining the outlines of the renal arteries where their margins are obscured by overlying bone shadows. Two examples are presented. Other applications of the subtraction technique are being investigated and are to be reported in the future.

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EXPERIENCE WITH AN AUTOMATIC TABLE FOR SERIAL PERIPHERAL VASCULAR ARTERIOGRAPHY*

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THERE is general agreement that automatic serial roentgenography is the best method for visualizing the peripheral vascular system.[1-15] A commercially available table (the Koordinate) for serial roentgenography, manufactured by the Elema-Schönander Company, has been in use at The New York Hospital for over a year. In this report, the advantages of the apparatus for the diagnosis of peripheral vascular disease are presented, and the disadvantages and improvements of the mechanism are discussed.

APPARATUS AND METHOD

The apparatus for automatic serial roentgenography of the peripheral vascular system consists of a motor driven table top which travels a distance of 10 inches for 4 successive movements (Fig. 1, *A* and *B*). In each position the table top comes to rest over a Schönander magazine permitting multiple exposures.[14] Interlocked with the table top stop positions are a series of micro switches which automatically drop the kv. p., approximately 7 kv. p. for each stop, for a total of 21 kv. p. For instance, for intravenous abdominal aortography and peripheral arteriography in the average patient, with a normal circulation time of 10 seconds,[16] the following program is usual: The first exposure is begun at the decholin circulation time, *i.e.*, 10 seconds. Five roentgenograms at intervals of 0.75 second are made of the abdominal aorta. To prevent blurring during movement of the table, the sixth slot in the Schönander magazine is not loaded with film. Three ex-

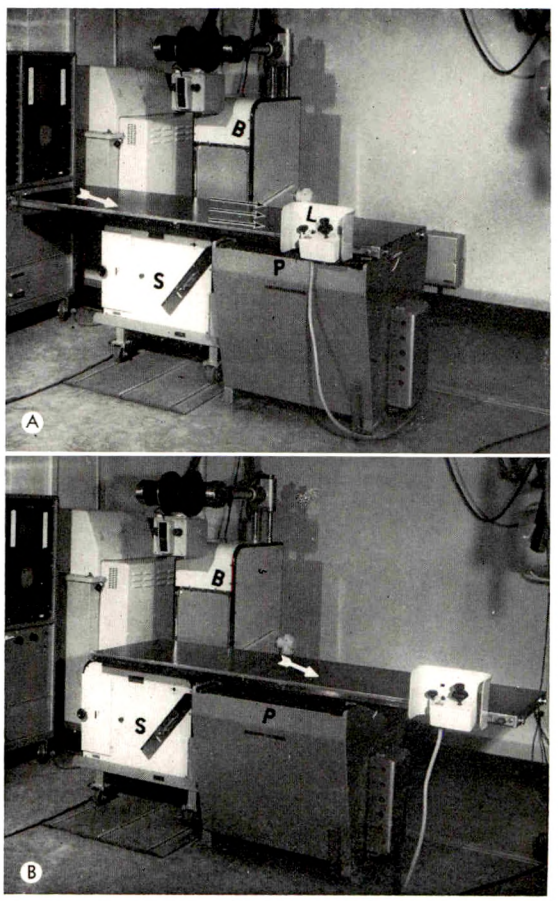


FIG. 1. *Photograph of automatic table top apparatus for serial angiography.* (*A*) The fully extended table (white arrow) moves cephalad (the patient is supine). The motor for moving the table is behind the panel (P); above, is the mechanism for locking the table top (L). The Schönander (S) serial film device is underneath the table top. The other Schönander magazine (B) for biplane study (when indicated) is above. (*B*) The position of the table top at the completion of the final (third) movement.

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posures at intervals of 0.75 second are then made of the aortoiliac arterial tree at the bifurcation of the abdominal aorta. Since another blank slot in the Schönander magazine has been introduced, 3 roentgenograms at 0.75 second each are made respectively of the superficial and deep femoral arteries. Finally, following another blank space (in place of film) in the Schönander magazine, roentgenograms of the lower superficial femoral and tibial arterial systems are completed. Accordingly, the total time of visualization of the abdominal aorta and peripheral arterial system is 12.75 seconds, 22.75 seconds after the beginning of the bilateral injections (Fig. 2, *A–D*). When the decholin circulation time is prolonged or when slowing of the peripheral vascular system is anticipated, as in abdominal aortic aneurysms, longer intervals between exposures may be made. For retrograde abdominal aortography via percutaneous femoral arteriography, injection of contrast material via the Gidlund syringe automatically initiates the exposure switch. A series of exposures for 4 movements for serial study of the peripheral vascular system can be programmed (Fig. 3, *A–D*). For example, the patient shown in Figure 3, *A–D* had a series of 5 exposures at intervals of 0.75 second which began 1 second after the onset of injection with the Gidlund

FIG. 2. *Serial intravenous abdominal aortograms and peripheral arteriograms of a 64 year old woman with intermittent claudication of the right leg and an expansile pulsatile abdominal mass.* (*A*) The arteriosclerotic abdominal aorta with thrombus (arrow), and an aneurysm below it. Note the markedly tortuous, but intact common iliac arteries. (*B*) Both common femoral arteries are also intact but on the right side, the superficial femoral artery is occluded at its origin (arrow). Only the hypertrophied deep femoral artery is opacified. (*C*) Only the lower end of the right superficial femoral artery (arrow) with collateral branches is visualized. Note the markedly narrowed and irregular but intact left superficial femoral artery. (*D*) The run-off into both legs, however, is good.

syringe. After blank intervals (obtained by not loading the sixth, tenth and fourteenth slots with film) a series of 3 roentgenograms respectively of the aortoiliac, iliofemoral and tibial arterial system was made. The total number of seconds for visualization of the peripheral vascular system after trigger of the Gidlund syringe injector was 13.75 seconds. Similarly, percutaneous injection of the femoral artery can be followed by serial study of one or more segments of the leg circulation (Fig. 5, *A* and *B*; and 6, *A*, *B* and *C*). In such instances, a single or at the most only two movements of the table need be made.

RESULTS

The automatic table herein described has been used for study of the peripheral vascular system ever since February 21, 1961. In well over 175 patients the peripheral vascular system was visualized after simultaneous bilateral intravenous injections.[16] In all of these, 4 movements of the table top were made, and the abdominal aortic, common iliac and femoral, superficial femoral, and popliteal arteries were opacified (Fig. 2, *A–D*). Fewer cases (35 patients) had peripheral arteriography via the percutaneous transfemoral passage of a catheter into the abdominal aorta (Fig. 3, *A–D*). This is because most of these patients were investi-

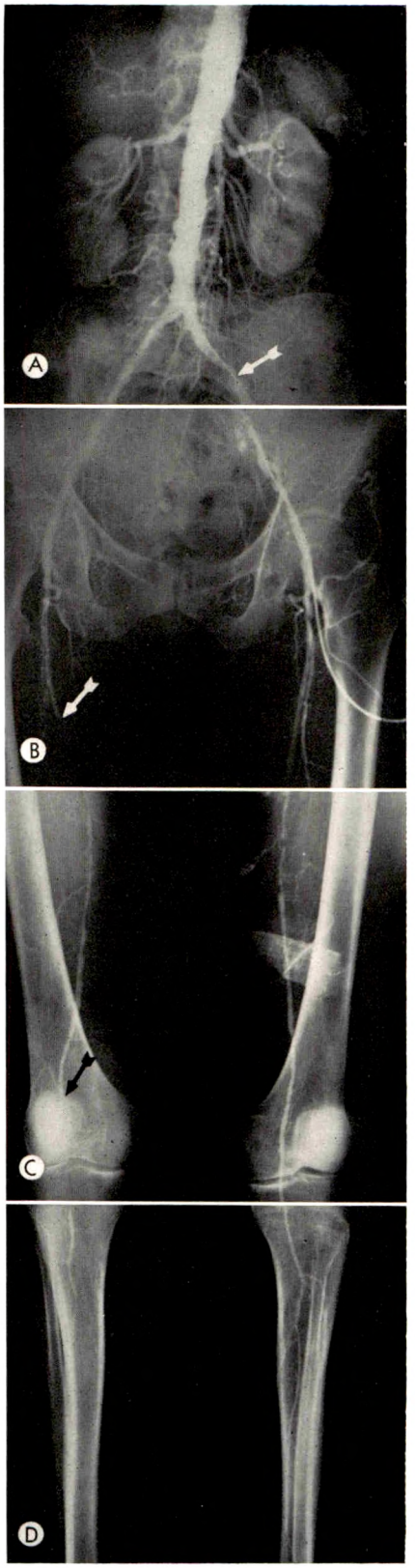
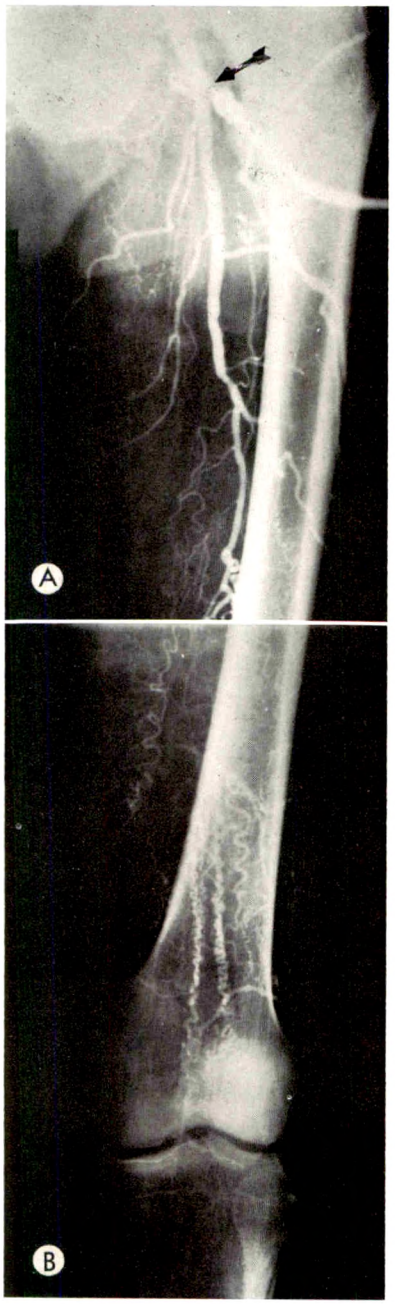


Fig. 3. *Serial abdominal aortograms and peripheral vascular arteriograms of a 56 year old woman with bilateral intermittent claudication. (Percutaneous transfemoral (Seldinger) technique was used for retrograde advance of the Odman catheter into the abdominal aorta, and injection was with the Gidlund syringe.)* (*A*) The abdominal aorta is markedly sclerotic. Note the severe narrowing of the left common iliac artery (arrow). (*B*) There is occlusion of the right superficial femoral artery (arrow). Note the collaterals over the left thigh. (*C*) Both common femoral arteries are narrowed; the left has small areas of segmental occlusion. The popliteal artery in the right side is occluded (arrow). (*D*) The run-off in the right leg is poor.



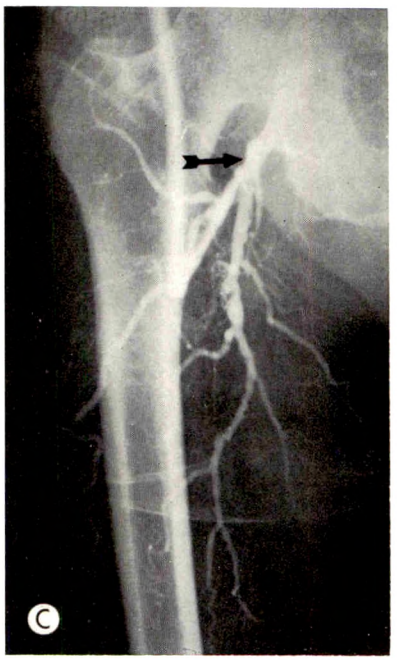


FIG. 4. *Percutaneous transfemoral arteriograms of a 78 year old man with intermittent claudication of both legs. (Previous intravenous abdominal aortography had disclosed a markedly tortuous arteriosclerotic aorta with intact common iliac and femoral arteries.)* (*A*) Injection of the left femoral artery via a needle (arrow) shows the markedly hypertrophied deep femoral artery with its collaterals. (*B*) After movement of the table, the poor run-off via collaterals is demonstrated. (*C*) The opposite (right) superficial femoral artery is also occluded. The needle with its plastic tubing is marked by an arrow.

gated for a renal arterial abnormality in order to find a renal vascular cause of hypertension.[6] Indeed, in practically all of these cases, the peripheral vascular system was intact as evidenced by palpable femoral arteries which allowed puncture of the artery and passage of the Seldinger wire and Odman catheter.[12,13] Transfemoral puncture and direct injection of contrast medium with serial roentgenography of the leg are illustrated in Figures 4 to 6 inclusive. In these patients, serial study of only two segments of the leg circulation was sufficient to outline the major peripheral circulation (Fig. 4, *A* and *B;* 5, *A* and *B;* and 6*B*). Studies of a single portion of the peripheral

vascular tree are shown in Figures 4*C* and 6*C*. In the case shown in Figure 6*C*, an exposure in the oblique projection of the popliteal aneurysm was also made in order to clear it from the overlying patella shadow.

DISCUSSION

The advantages of serial roentgenography of the peripheral vascular system are obvious.[1–16] For instance, multiple exposures of the abdomen when an aortic aneurysm is suspected are better than a single roentgenogram because blood flow in such an arteriosclerotic vessel is markedly slowed so that the chances of visualizing the lesion in its entirety are greater when many exposures are made. Particularly in the aortoiliac and iliofemoral arterial systems, multiple serial roentgenograms permit not only the demonstration of arterial stenosis and occlusions, but also demonstrate the effectiveness of collateral circulation, the rate of blood flow, and the pattern of the circulation in the extremities.

The disadvantages of the automatic table, aside from its expense and an inherent delay in the onset of exposure which must be ascertained for effective use of the serial exposures, have chiefly to do with inability to adjust the kilovoltage according to the thickness of each part of the lower extremity. As presently constituted, the settings for exposure of the abdomen govern the roentgenography of the lower

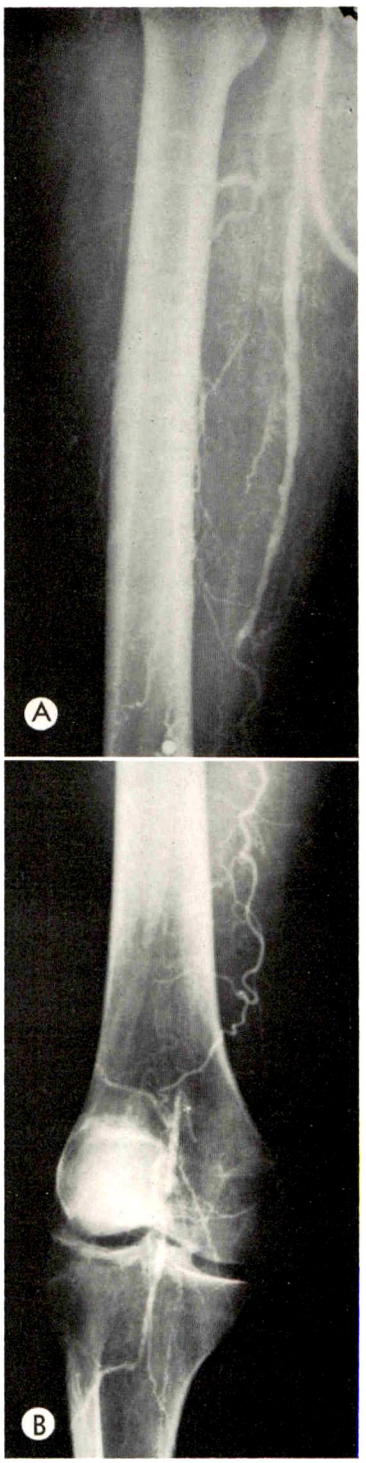


Fig. 5. *Percutaneous transfemoral arteriograms of a 60 year old diabetic woman with ischemic necrosis of the right big toe.* (*Previous intravenous abdominal aortography had disclosed an intact abdominal aorta and iliofemoral arteries.*) (*A*) After injection of the right femoral artery via a No. 18 gauge needle, the tortuous, markedly narrowed, and occluded superficial femoral artery is demonstrated. Note the rather poorly developed collateral circulation. (*B*) After movement of the table, the lower end of the right superficial femoral artery just above the knee is visualized. Below the popliteal artery, the run-off is poor.

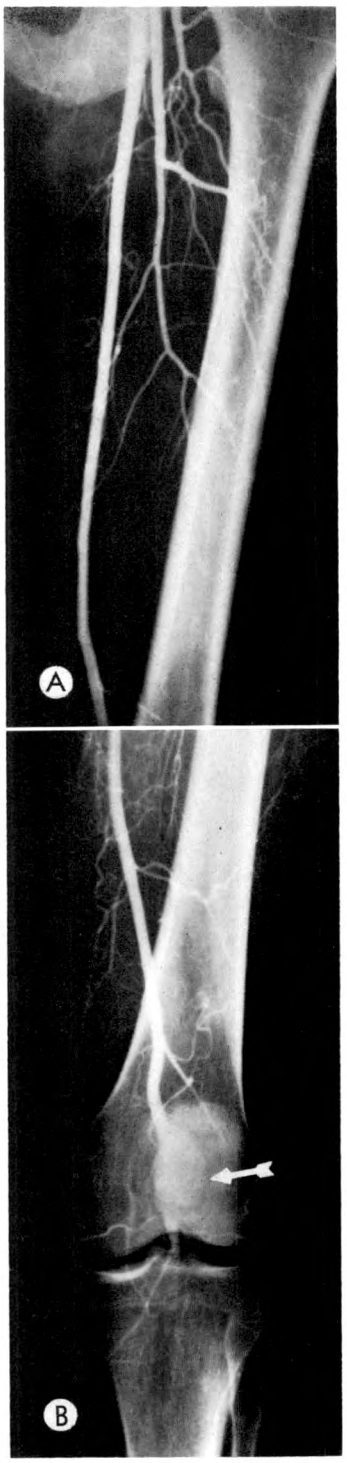




FIG. 6. *Left popliteal aneurysm in a 51 year old woman with advanced rheumatic heart disease, mitral stenosis, and tricuspid regurgitation. (Intravenous abdominal aortography had previously disclosed an intact abdominal aorta and iliofemoral arteries.)* (*A*) Percutaneous transfemoral injection of the left femoral artery disclosed an intact superficial femoral artery. (*B*) After the first series of roentgenograms, the popliteal artery aneurysm (arrow) was visualized. (*C*) Another study with the leg placed obliquely, in order to remove the shadow of the overlying patella, showed the aneurysm with abrupt occlusion of the vessel below it. Note the adequacy of the collaterals. (This patient, was referred by Dr. Laurence Miscall who obtained an excellent result after excision of the aneurysm and ligation of the popliteal artery proximally, but without disturbing the collateral circulation.)

limbs. Arbitrary drop of kilovoltage (7 kv.) after the initial series of abdominal roentgenograms sometimes results in overexposure or underexposure of the lower extremities. The length of the exposures with the present apparatus is also limited to 0.2 second. While this fast exposure technique enhances visualization of the renal arteries,

it does not permit the intense opacification of the abdominal aorta and its branches which can be secured with a 2 to 3 second exposure time with the single exposure technique.[16] However, the excellent opacity may not be entirely due to the increased exposure time; for, with the single film method, the use of the Bucky grid for the abdominal aortic study and a grid-cassette for the extremity provides vascular opacification which is apparently superior to that of the Schönander grid-cassette system.

Mechanical readjustment of the apparatus to permit flexible variations of the kilovoltage will also permit roentgenography of the thoracic cardiovascular structures if desired, and then the abdomen, pelvis and lower extremities. This will allow visualization of the cardiovascular structures as well as the peripheral vascular system.

SUMMARY AND CONCLUSIONS

An automatic commercially available table in use for over a year at The New York Hospital permits serial visualization of the entire peripheral vascular system. Double, simultaneous, intravenous injections or a single injection with a Gidlund syringe, of the abdominal aorta via the percutaneous transfemoral retrograde abdominal aortic route can be used to opacify the aortoiliac and iliofemoral arterial tree. Similarly, serial translumbar aortography or direct femoral arteriography can be achieved by direct percutaneous abdominal aortic or femoral arterial injections.

The advantage of the apparatus lies in the ability to move the patient over a Schönander magazine so that progressive serial roentgenography of the peripheral vascular system can be secured. In order to enhance the technique, mechanical adjustment of the apparatus to permit flexibility in selection of the kilovoltage for each part of the peripheral vascular system is desirable. This will also allow visualization of the abdominal aorta and peripheral vascular system following opacification of the cardiovascular system and bring nearer the goal of total body angiography—visualization of the entire cardiovascular system when indicated, with a single bolus of contrast agent.

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PLESIOSECTIONAL TOMOGRAPHY OF THE TEMPORAL BONE

A NEW MULTI-SCREEN CASSETTE

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IN 1948, de Abreu[1] published an important advance in tomographic technique. This method of examination is now generally known as simultaneous multi-section or multi-layer tomography. The object of the technique is to produce, by one exposure only, a series of consecutive tomograms each recording a separate body layer. This is done by substituting for the conventional cassette used in normal tomography a special magazine containing several films. These multi-section magazines are commercially available with film separators or spacers made of polyester foam or balsa wood of from 0.5 to 1.0 cm. in thickness.

In normal tomography, only the body layer in the same plane as the fulcrum is sharply recorded on a film. In multi-section tomography, however, the first film in the magazine is situated at the level of this plane and records the body layer at this fulcrum level. The other films in the magazine are placed at successively lower levels and record layers of the body below the fulcrum level.

In 1950, Sans and Porcher[3] designed a laminagraph called the Polytome, which made it possible to obtain body-section layers of high diagnostic quality as thin as 1 mm. of thickness. However, we felt that films of body sections of a thickness of 1 mm. could be obtained with conventional tomographic equipment, but using a special multi-screen cassette.

The multi-screen technique for plesiosectional tomography adapts quite well to examination of the temporal bone and we are thus able to get better visualization of the complicated structures of this region. Since the various structures of the petrosa are confined to a small area, the amount of separation of the films in the multi-screen cassette would have to be of the same small order. The Polytome laminagraph can accomplish the body-section layers of the required order, but from 6 to 10 exposures are needed. With a multi-screen cassette, however, cuts in the order of 1 mm. can be obtained with conventional tomographic equipment using two exposures in most instances.

With multi-section tomography, the space or distance between the sharply recorded layers of the body is slightly less than the distance between the films separated by the polyethylene foam in the cassette magazine. Since the film separation is known, the separation of the body layers can be calculated by the following expression:

$$S_L = S_F \left(\frac{D}{D+d} \right).$$

Alternately, the film separation needed to give the desired amount of body layer separation can be found from the following expression:

$$S_F = S_L \left(1 + \frac{d}{D} \right).$$

In both expressions:

S_L = separation between body layers in centimeters
S_F = separation of films in centimeters
D = focus to fulcrum distance in centimeters
d = distance of fulcrum to first film in centimeters

The uppermost film in the cassette receives the most radiation with the ones below receiving successively less because of the interposed screens and films and to a lesser degree a gradually increasing dis-



FIG. 1. Multi-screen cassette for use in plesiosectional tomography.

tance. These effects of absorption and distance can be compensated by the use of intensifying screens of progressively higher speed from top to bottom of the cassette. The proper combination of screens will depend on the kilovoltage used and the amount of film separation.

With the new technique, a set of intensifying screens, consisting of four pairs of matched screens, were carefully mounted in a conventional cassette to ensure uniform contact (Fig. 1). No spacers were added, since the screens alone provided the required separation of about 1 mm. between the levels (Fig. 2).

The Siemens Universal tomograph was used. A lead diaphragm added to the multileaf collimator restricts the roentgen-ray beam to a size of $4\frac{1}{2} \times 5\frac{1}{2}$ inches. In addition, a lead shield with a 5×6 inch aperture was placed in the space between the conventional Bucky tray and the undersurface of the table to reduce film fogging by secondary radiation.

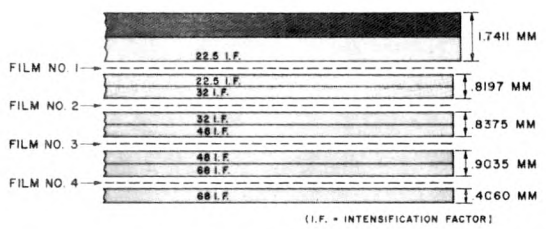


FIG. 2. Schematic drawing of screens in cassette, showing separation and intensification factor of screens.

Positioning was accomplished by having the patient lie supine with the median plane of the head vertical to the table. The head was so adjusted that a line projected from the outer canthus of the eye to the tragus of the ear would be perpendicular to the roentgenographic table. The central ray was directed through a point located one-fourth inch medial to the outer canthus of the eye and should pass through the petrosa at the level of the tip of the tragus (Fig. 3). Two exposures of the petrosa on the affected side are necessary to include 6 to 8 mm. of tissue. These are made on the upper two positions of quartered 10 by 12 inch films. The same technique should be used for the opposite petrosa in the lower half of the quartered 10 by 12 inch films for comparison purposes.

Anteroposterior tomography of the normal temporal bone (Fig. 4, *A–F*) will include on the most ventral cut, taken at the level with the tip of the tragus, the external auditory meatus (1) as the most characteristic structure. This may be used as an anatomic point of reference for the initial study of the tomogram. Other visualized structures are the malleus (2), the cochlea

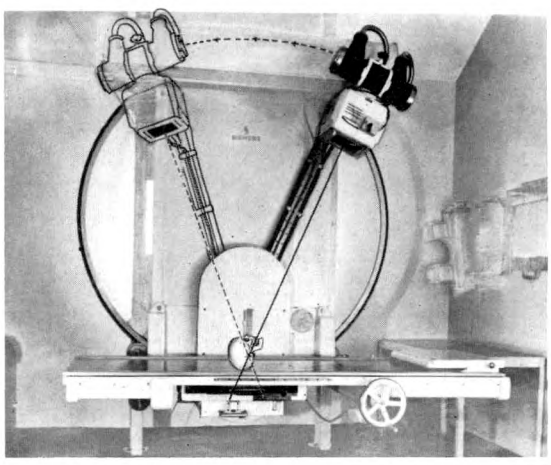


FIG. 3. Tomographic apparatus showing position of skull.

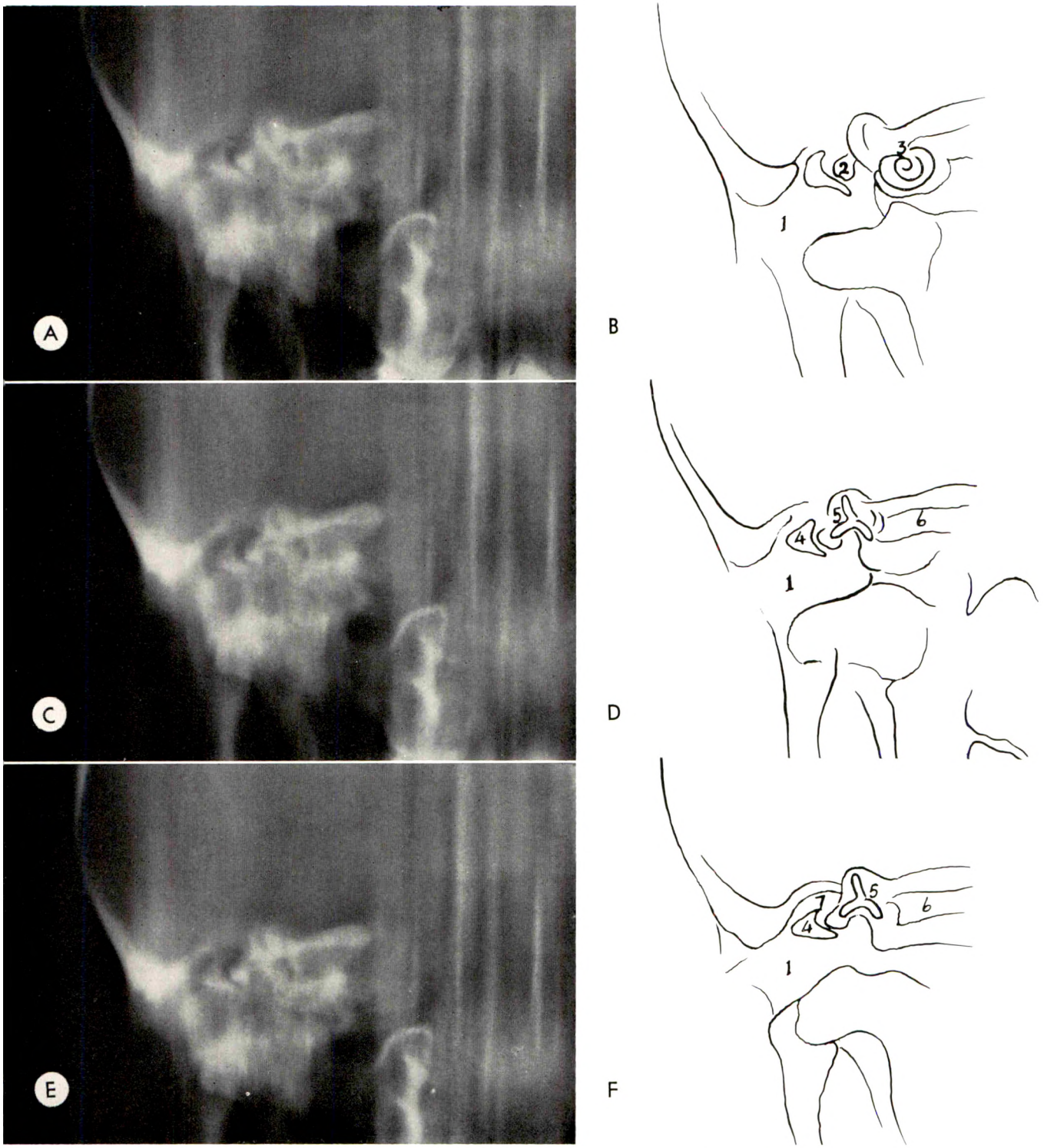


Fig. 4. (*A–F*) Three tomographic cuts with *A–B* as most ventral and *C–D* and *E–F* at successive levels below. The external auditory meatus (1). Other visualized structures are the malleus (2), the cochlea (3), the incus (4), the semicircular canals (5), the internal auditory canal (6) and the antrum (7).

(3), the incus (4), the semicircular canals (5), the internal auditory canal (6) and the antrum (7).

SUMMARY

A new multi-screen cassette for plesiosectional tomography to be used with conventional tomographic equipment has been described. The structures seen in normal tomographic cuts of the petrosa have been mentioned.

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THE USE OF PLESIOSECTIONAL TOMOGRAPHY IN THE DIAGNOSIS OF EIGHTH NERVE TUMORS

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IN 1961, a new tomographic technique, plesiosectional tomography, was developed by McGann[10] using a specially designed cassette with which good detail of the small anatomic structures of the temporal bone can be obtained. It has proven to be a very practical adjunct to the routine studies since only conventional tomographic equipment is needed. Four pairs of special intensifying screens of progressively higher speed were made and were mounted in a conventional cassette. These screens vary from 0.4098 mm. to 0.4517 mm. in thickness and in themselves give the required separation of the four sheets of film. A single exposure covers a total depth of 4 mm. of tissue. The resulting tomograms give a clear delineation of the complex structures around the internal ear without the use of expensive and specialized tomographic equipment.

For many years the presence of eighth nerve tumors has been determined by plain roentgenograms of the skull.[7] In the early years of roentgenologic diagnosis, considerable bony change was usually present by the time the diagnosis of these lesions was made. This was due to frequent delay in the treatment of symptomatic patients. An average symptom duration of 4 to 5 years was not unusual. In a series reported by Gonzalez-Revilla,[5] 86 per cent presented with cerebellar symptoms and 47 per cent of the cases had increased intracranial pressure.

While occasional patients still present themselves with a long history of unilateral deafness, tinnitus, or even increased intracranial pressure, many cases, in recent years, have been referred for roentgen examination when unilateral hearing loss is the only symptom. Wider interest and knowledge of this problem among otolaryngologists, as well as the availability of audiometric techniques such as Von Bekesy's and pure tone audiometry have resulted in earlier patient evaluation by neurosurgeons and radiologists. Secondary bony changes are less likely to be present in this group and when found are often less extensive than in the earlier reported series. Small changes may be visualized with the Chamberlain-Towne and Stenvers projection. Further evaluation of this area has been possible with the use of tomography. The development of the Polytome allowed the most detailed and accurate study to date of the temporal bone with particular reference to the middle and inner ear.[1,14] Equivalent results are now possible with plesiosectional tomography with much less expense and technical difficulty.

Anatomic findings in normal patients and diagnostic features of eighth nerve tumors seen on plain roentgenograms of the skull have been reported in the past and are worthy of a brief review. Symmetry of the internal auditory canals is present in 40–67 per cent of normal skulls. There is considerable variation between individuals and between the petrous portions of the temporal bone in the same individual.[8] The average width of the internal auditory canal in a series of 500 normal cases reviewed by Camp and Cilley[2] was 5.23 mm. with a range of 2.5 to 11 mm. The usual difference in the width of the canal in the same patient is within 1.5 mm., although larger variations have been described.[2] In 1942 Schwartz[13] reported changes in the canal in patients with acoustic neuromas. These included early atrophy and demineralization of the posterior wall of the canal, enlargement of the porus, development of a notch-like defect in the petrous ridge and destruction of the entire petrous apex. The

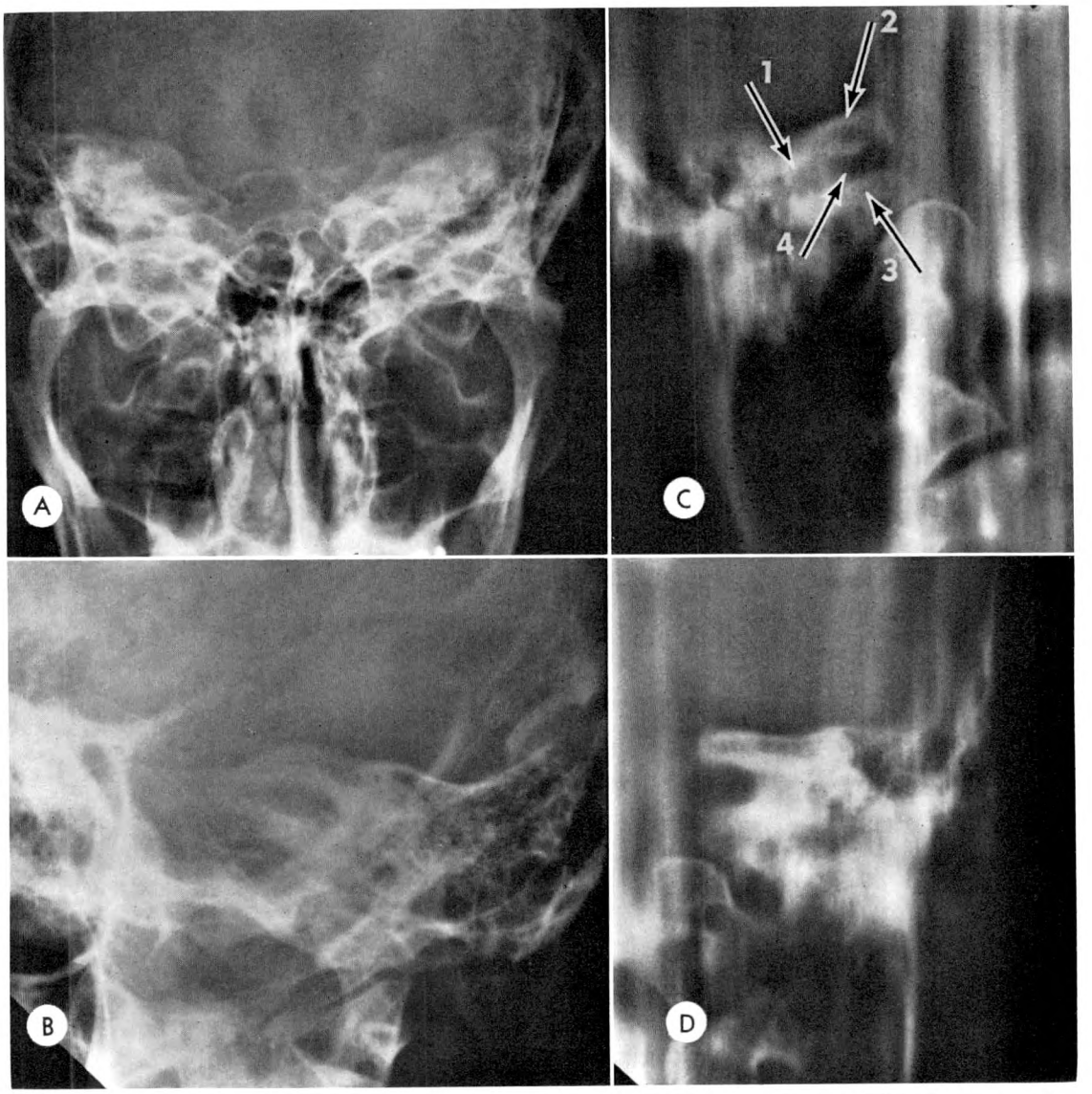


FIG. 1. R.P., a 36 year old male with hearing loss in the left ear for 8 years. (*A*) Chamberlain-Towne view shows slight widening of the left internal auditory canal and of the meatus. (*B*) Stenvers view shows similar findings. (*C*) Normal right plesiosectional tomogram: 1. Internal auditory canal. 2. Suprameatal region. 3. Inframeatal region. 4. Internal acoustic meatus or porus. (*D*) Left plesiosectional tomogram showing bony changes with greatest clarity. Note widening and shortening of the internal auditory canal, widening of the meatus and erosion of the suprameatal and inframeatal regions.

configuration of the canal has also been described in normal skulls as either oval or rounded.[2] Space-taking lesions in the region of the internal auditory meatus may cause a funnel-shaped configuration of the canal as seen in the frontal projections. In the submentovertex or base view of the skull, the funnel-shape at the porus can be normal.[12] Generalized widening of the internal auditory canal is also seen with lesions of the eighth nerve. In previously reported cases, bone destruction usually has been first detected posteriorly with apparent shortening of the canal and later superiorly with erosion of the suprameatal region. This can be difficult to evaluate because of

frequent asymmetry in the suprameatal region inasmuch as pneumatization may be present on one side only with dense bone on the opposite side in a normal skull.

In the past, the percentage of patients showing bone changes on plain roentgenograms in cases of acoustic nerve tumor has varied from 30 to 90 per cent. Most authors have noted that approximately 50 per cent of their known cases do have recognizable bony changes.

At the present time our usual roentgenographic examination for suspected lesions of the eighth nerve consists of stereoscopic posteroanterior, Chamberlain-Towne and lateral views. Stenvers projections and occasional submentovertex views are also obtained. Plesiosectional tomographic examination of the petrous portions of the temporal bones are then performed on all cases. Both the Stenvers and Chamberlain-Towne projections have been disappointing when compared to plesiosectional tomography. Several of our recent cases showed marked bony change on tomograms while the routine roentgenograms were either normal or of questionable significance. Partial pneumoencephalography is used as a supplemental examination for questionable cases since some tumors may be predominantly intracranial and thus not produce any appreciable bony change.

Since January, 1962, when the use of plesiosectional tomography was instituted, we have examined 6 proven cases of eighth nerve tumor by this method (Fig. 1–6).

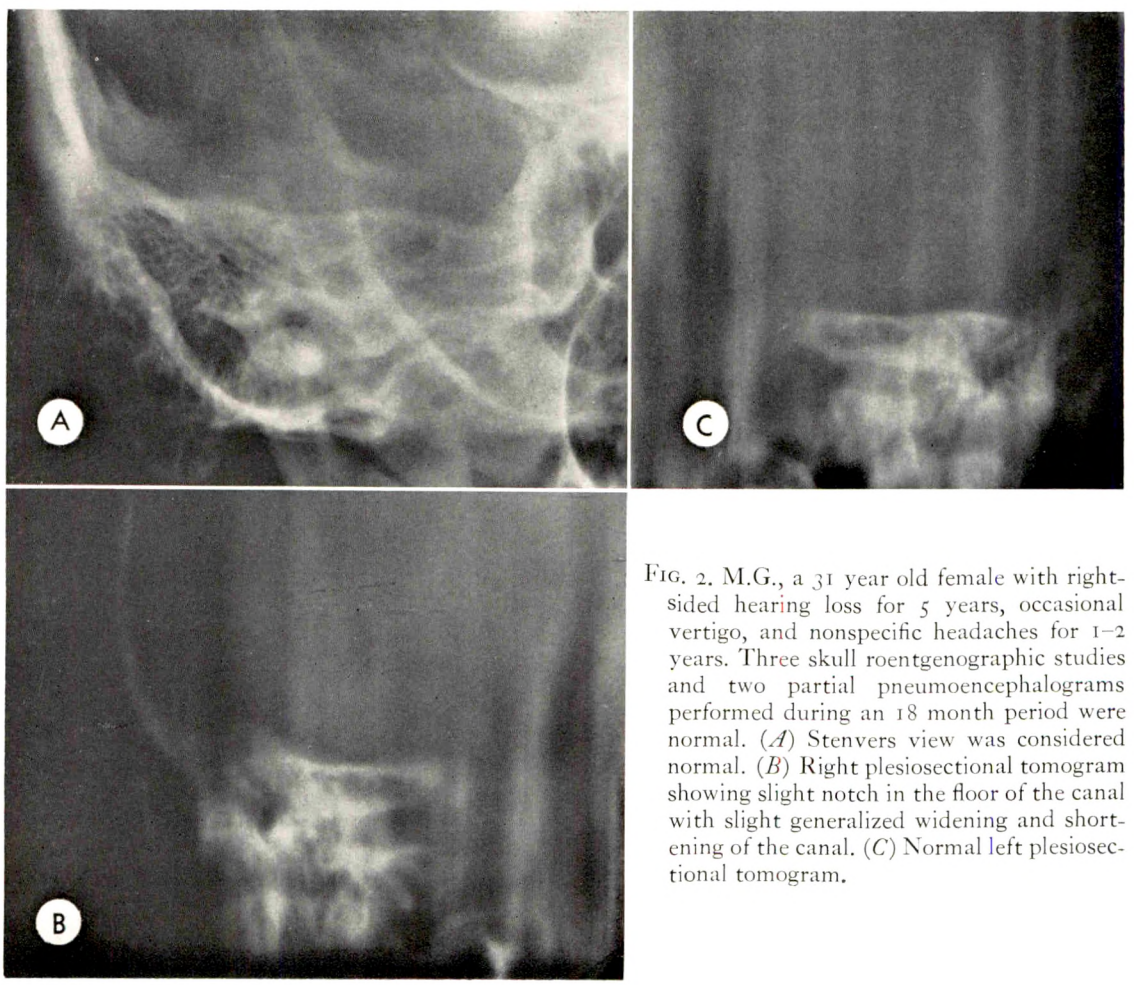


Fig. 2. M.G., a 31 year old female with right-sided hearing loss for 5 years, occasional vertigo, and nonspecific headaches for 1–2 years. Three skull roentgenographic studies and two partial pneumoencephalograms performed during an 18 month period were normal. (*A*) Stenvers view was considered normal. (*B*) Right plesiosectional tomogram showing slight notch in the floor of the canal with slight generalized widening and shortening of the canal. (*C*) Normal left plesiosectional tomogram.

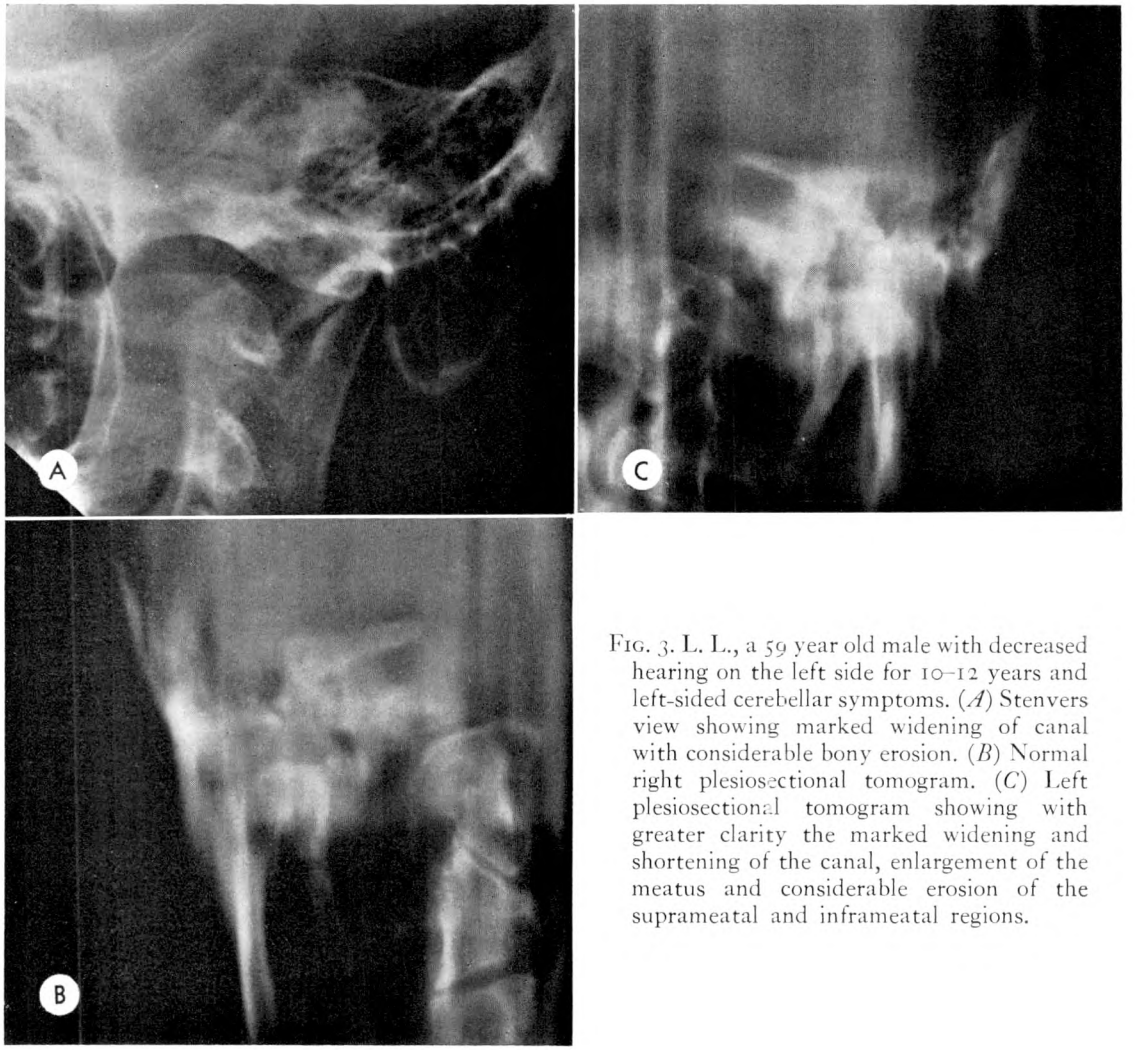


FIG. 3. L. L., a 59 year old male with decreased hearing on the left side for 10–12 years and left-sided cerebellar symptoms. (*A*) Stenvers view showing marked widening of canal with considerable bony erosion. (*B*) Normal right plesiosectional tomogram. (*C*) Left plesiosectional tomogram showing with greater clarity the marked widening and shortening of the canal, enlargement of the meatus and considerable erosion of the suprameatal and inframeatal regions.

Plesiosectional tomograms have shown bony changes in all of these cases. The earliest lesion in this series presented with a small notch in the floor of the internal auditory canal with slight but definite generalized widening of the canal as compared to the opposite side. These changes could not be appreciated on 3 previous routine skull roentgenographic examinations, including the Stenvers view. Two partial pneumoencephalograms with particular attention to the cerebellopontine cisterns were normal. The other cases all showed varying degrees of bony change. Generalized widening of the canal was seen in several cases. The classic "funnel shape" of the porus acusticus was also noted in 3 of the cases. Erosion of the suprameatal region formed the superior edge of the funnel in these lesions. Five of the cases had erosion of the floor of the canal just at the porus, making up the inferior margin of the funnel. This was noted in 2 cases where superior erosion was not demonstrable. In one case this area of bone destruction was contiguous with destruction of most of the petrous apex. Apparent shortening of the internal auditory canal was noted in all of the cases. This is caused by erosion of the thin posterior wall of the canal.

Most, but not all, of the bony changes could be demonstrated to some extent by

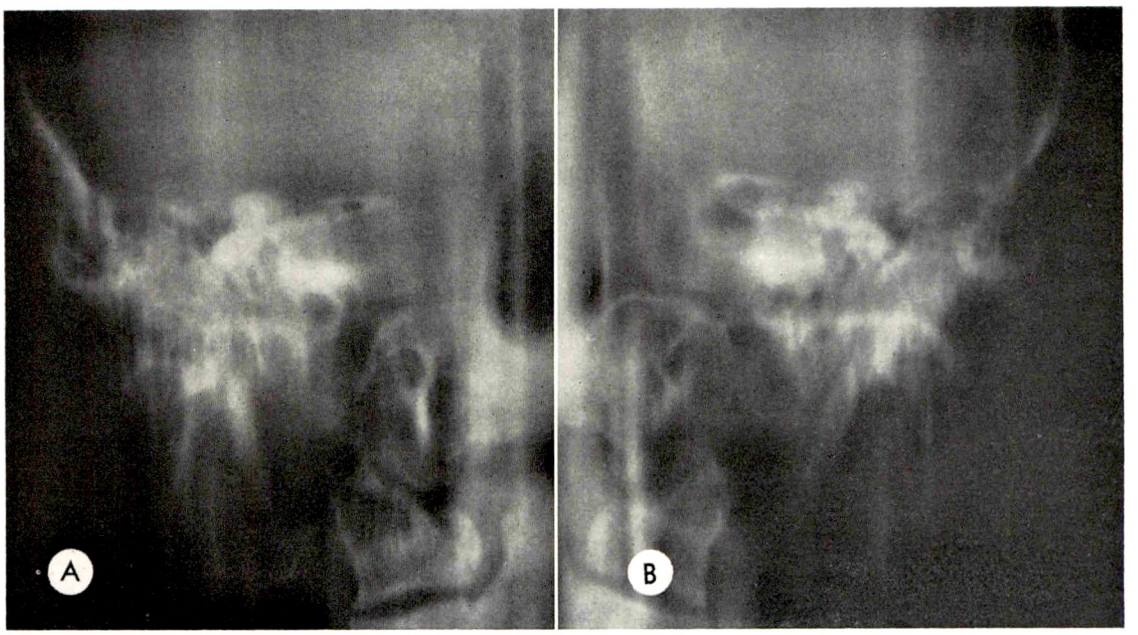


Fig. 4. E.R., a 54 year old male with right-sided hearing loss for 8 years. (*A*) Right plesiosectional tomogram showing classic funnel-shaped appearance with widening and shortening of the canal, erosion of the suprameatal and inframeatal regions. (*B*) Normal left plesiosectional tomogram.

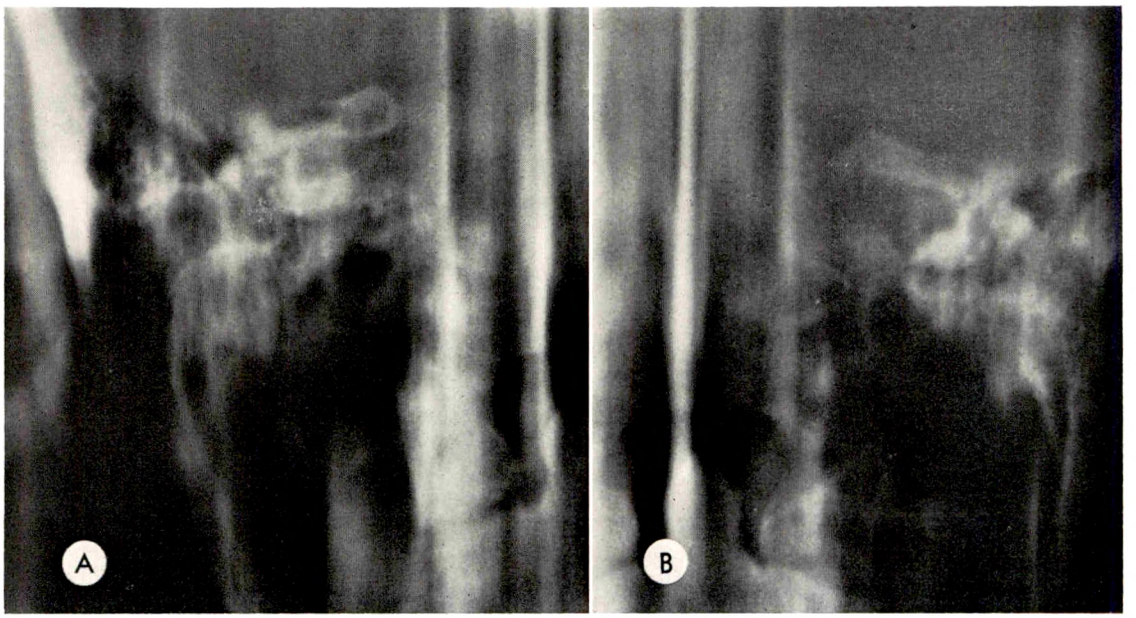


Fig. 5. S.W., a 59 year old male with 2 year history of left-sided hearing loss and slight left cerebellar signs. (*A*) Normal right plesiosectional tomogram. (*B*) Left plesiosectional tomogram with marked destruction of bone in the inframeatal region and petrous apex. The suprameatal region appeared normal except for slight irregularity of the tip.

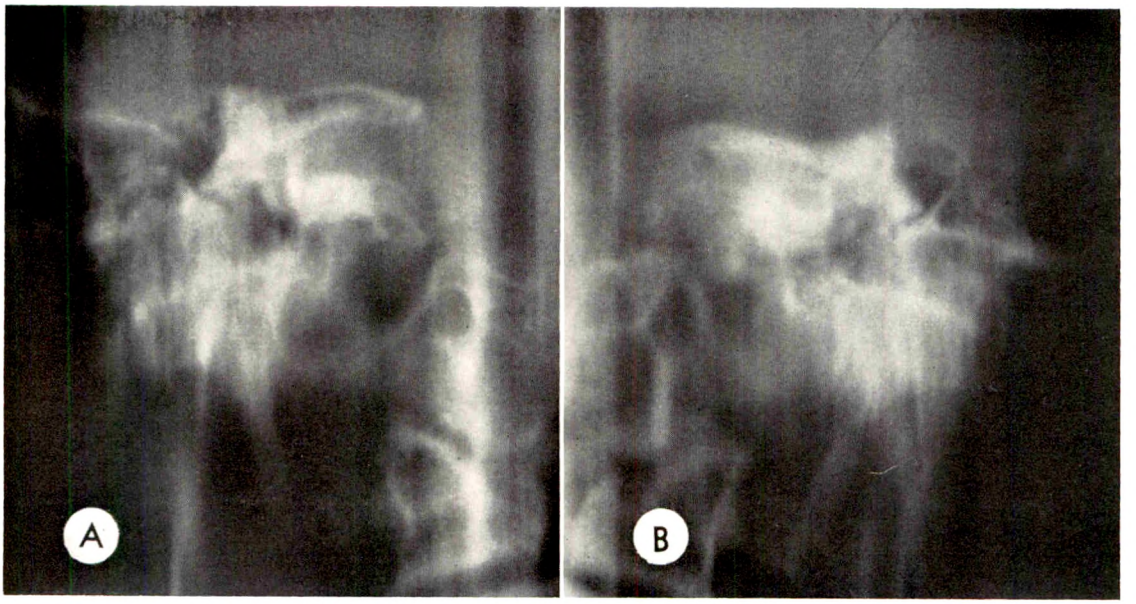


FIG. 6. H.S., a 52 year old male with hearing loss for 22 years and poor balance for 10 years. He had increased cerebellar symptoms for the past 6 months. (*A*) Right plesiosectional tomogram showing generalized widening and shortening of the canal and widening of the meatus. Note the good pneumatization of the involved side as compared to the lack of pneumatization in this region on the normal side. (*B*) Normal left plesiosectional tomogram.

the conventional roentgenographic examinations. The clarity of detail visualized on plesiosectional tomograms, however, could not be approached by routine studies. We feel, therefore, that the additional information obtained warrants the use of this examination in all suspected cases of eighth nerve tumor or any lesion of the temporal bone.

SUMMARY

The new technique of plesiosectional tomography using conventional equipment has proven to be of considerable value in temporal bone disease, particularly in the diagnosis of acoustic neuromas. It is recommended for routine use in all cases of suspected tumors in the region of the internal auditory canal.

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A CLINICAL INVESTIGATION OF A NEW CARDIOVASCULAR CONTRAST AGENT, DIATRIZOATE SODIUM AND DIPROTRIZOATE (DITRIOKON)*

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THE first study of the heart and great vessels in the living man with the injection of an organic iodine compound, sodium iodomethamate (uroselectan), was published by Forssmann[6] in 1931. Since then a large number of contrast media have been and still are being introduced, which indicates that the ideal agent has not yet been found.[1] Skiodan and hippuran,[17] diodrast,[18] neoiopax,[2] urokon,[3] miokon,[12] cardiografin,[9] and hypaque[10] are media that have been used for angiocardiography.

The number of angiographic studies being performed in recent years has increased as a consequence of the introduction of selective angiography with rapid serial roentgenography and cine-angiography. The possibility of an adverse reaction is increased when an opaque substance is injected in concentrated amounts particularly when close to the pulmonary parenchyma or the coronary arteries.[11,13] The ideal contrast medium should be nontoxic, have a viscosity low enough to permit rapid manual and mechanical injection and give adequate visualization of the heart or other vascular structures.

In the present study a new contrast medium, a solution consisting of a mixture of 36.7 per cent diatrizoate sodium and 31.4 per cent diprotrizoate* (weight per volume) was evaluated. Specific attention was given to certain properties, namely ease of injection, incidence of side-effects and quality of the angiograms.

* Product of Mallinckrodt Chemical Works, St. Louis, Missouri.

METHODS

Right heart catheterizations were performed on patients with congenital heart disease. The retrograde aortographic examinations were carried out primarily on adult patients with acquired cardiovascular disease or essential hypertension. The age of the patients ranged from 2 weeks to 83 years; their weights ranged from 6 to 214 pounds. One hundred seventeen of the patients were male and 99 were female.

Premedication consisted of the subcutaneous administration of morphine sulfate, 0.1 mg. per pound of body weight (maximum dose: 15 mg.) and sodium phenobarbital, 6.0 mg. per pound of body weight (maximum dose: 200 mg.). Hydroxyzine hydrochloride,* 1.0 mg. per pound of body weight (maximum dose: 100 mg.) was given intramuscularly immediately before the beginning of the catheterization. No general anesthesia was used.

The procedure was performed under fluoroscopic and television control using the North American Philips 5 inch image amplifier. Continuous electrocardiographic oscilloscopic monitoring was maintained and periodic photographic recordings were made during the procedure. Images of the electrocardiograms were incorporated into the cine-angiocardiograms in many cases by the technique used in this laboratory.[14]

The cine-angiograms were made with a 16 mm. or 35 mm. camera at the usual speed of 60 frames per second. Occasion-

* Supplied as Vistaril by Charles Pfizer and Co., Inc.

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This work was supported by grants from the Missouri and St. Louis Heart Associations.
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‡ Assistant Professor of Clinical Medicine and Director of the Division of Cardiac Catheterization, St. Louis University School of Medicine.

ally, a camera speed of 30 or 128 frames per second was employed.

The diagnostic quality of angiograms is the result of many factors, such as the rapidity of injection, the quantity of contrast medium used, the rapidity of dilution by large intracardiac shunts, heart rates and proper exposure of the film. The angiograms were classified as satisfactory or unsatisfactory with these factors in mind.

The mixture of diatrizoate sodium and diprotrizoate (ditriokon) was heated to body temperature prior to injection. No tests were performed for sensitivity reaction. The injections were usually made manually in infants and small children. A modification of the Lehman mechanical injector[7] was used in patients requiring more than 8 ml. of contrast medium. The average duration of the injections was 2.0 seconds, the range being 0.5 to 3.0 seconds. The cardiac catheters employed had 4 or 6 side openings near the tip. Catheter sizes ranged from 5F to 9F, the largest being used when feasible. Retrograde aortography was performed by the Seldinger technique.[20] The usual quantity of contrast medium per injection was 0.3 to 0.5 ml. per pound of body weight, the injection doses ranging from 2 to 45 ml. (the limiting capacity of the syringe). Two or more injections of contrast medium were made in 96 patients and as many as 4 consecutive injections were made in 18 patients. Several have had 6 injections during one catheterization. When more than one injection was made during a catheterization, a minimal interval of 10 minutes was allowed to permit some clearance of the medium from the blood. There were 297 angiographies made by selective injection with right heart catheterization. Retrograde arterial angiographies were performed in 87 instances.

The patients were advised of the impending sensation of flushing or warmth following the injections. Close observation was made for the occurrence of immediate and late side effects, such as nausea, vomiting, dyspnea, coughing, flushing, tightness in the chest, headache, syncope, sneezing, urticaria, cardiac arrhythmias, shock reactions or electrocardiographic changes.

RESULTS

The viscosity of the mixture diatrizoate sodium and diprotrizoate (ditriokon) is lower (Table 1) than that of most other media and less manual effort was necessary to inject the medium. This was a subjective conclusion.

Warm or flushing sensations were experienced by nearly all patients. Mild coughing occurred infrequently and lasted only a few seconds. Significant changes in the electrocardiogram were seen in 2 cases. In one, atrial tachycardia increased from 120 to 190, with appearance of S-T segment depression and T wave inversion on the electrocardiogram. These changes disappeared gradually over a 30 minute period. The other case, a 33 pound 2 year old boy with Ebstein's anomaly, had a 15 ml. injec-

Table I

COMPARATIVE FEATURES OF ANGIOGRAPHIC CONTRAST MEDIA

Contrast Medium	Iodine Content	Viscosity (c.p.s.)	
		25°C.	*37.5°C.*
Sodium Acetrizoate (Urokon)	46%	4.6	3.0
Diatrizoate Methylglucamine (Cardiografin)	40%	23.0	13.0
Diatrizoate Sodium and Methylglucamine (Hypaque-M, 90%)	46%	39.0	21.0
Diprotrizoate (Miokon-50)	57%	4.0	2.6
Diatrizoate Sodium and Diprotrizoate (Ditriokon)	40%	8.4	5.5

Note: Data provided by Mallinckrodt Chemical Works, St. Louis, Missouri.

tion of medium into the inferior vena cava in 2 seconds. His heart rate immediately rose from 120 to 170, but remained regular. The electrocardiogram revealed a rapid decrease in voltage, the QRS complex changing from 15 mm. to 4 mm. in amplitude. The electrocardiogram gradually returned to normal within 10 minutes. In nearly all patients moderate increases in heart rate developed immediately after the injections. This increased heart rate did not persist for more than 1 minute.

Disorientation for a few moments followed the retrograde injection of 40 ml. of contrast medium into the arch of the aorta of a 54 year old male patient, who had left hemiparesis with clinical evidence of recurrent carotid artery insufficiency. Nystagmus was present for 2 to 3 minutes. These side-effects cleared with no sequelae.

In the one case where the Radner suprasternal approach[16] was used, 10 ml. of contrast medium was accidentally injected into the wall of the ascending aorta. Immediate withdrawal of most of the medium was possible and no symptoms were observed. Subsequent chest reontgenograms did not reveal evidence of contrast medium in the wall. The patient died 3 weeks later of cardiac insufficiency secondary to the following cardiac lesions: pulmonic stenosis, atrial and ventricular septal defects and rheumatic heart disease with aortic insufficiency. Autopsy confirmed the diagnosis and revealed evidence of a 2 by 2 cm. hemorrhagic plaque in the intima of the ascending aorta. No contrast medium was seen on the roentgenogram of the specimen.

A left atrial injection of 4 ml. of the mixture diatrizoate sodium and diprotrizoate was made in a 1 month old, 8 pound patient with mitral atresia, atrial septal defect, ventricular septal defect, coarctation and patent ductus arteriosus continuing as the descending aorta. The patient was on oxygen and the saturation by ear oximetry was 75 per cent. The respirations ceased and the heart rate dropped from 140 to 40 within approximately 1 minute after the injection. External cardiac massage and intubation were instituted and isoproterenol was given. The cardiac rate returned to normal in 20 minutes. The patient was connected to a respirator and attempts to remove the infant from it always resulted in respiratory distress. A roentgenogram of the chest showed complete opacification of the lungs due to severe pulmonary edema. Although the lung fields gradually cleared over a 10 day period, the patient subsequently expired. Microscopic examination revealed the lungs to be normal.

Evaluating the quality of angiograms is always subject to many factors. All the angiograms obtained in this series were considered adequate for diagnostic evaluation. In comparing these with cine-angiograms using another contrast medium, diatrizoate sodium and methylglucamine (hypaque-M, 90 per cent), no significant difference could be appreciated.

DISCUSSION

Three hundred and eighty-four angiographies were performed on 216 patients employing the mixture diatrizoate sodium and diprotrizoate (ditriokon). One hundred and seventy-three patients had angiography by right heart catheterization, 3 had the procedure repeated and one had 2 retrograde aortographic examinations. Forty-three of the 216 patients had retrograde aortography and one had the procedure repeated. All of the patients having right heart catheterization had congenital heart disease, while those having retrograde aortography had essential hypertension or cerebral vascular insufficiency.

It is significant that the viscosity of this preparation (Table 1) at 25°C. and at 37.5°C. is 8.4 and 5.5 centipoises per second, respectively. This decreased viscosity has been achieved by a solution of 36.7 per cent diatrizoate sodium and 31.4 per cent diprotrizoate weight per volume. The total organically bound iodine content is 40 per cent (0.4 gm./ml.). The low viscosity of this mixture permits easier manual injection and is an outstanding property of the preparation. Excellent studies on the vis-

cosity of contrast media affecting the rate of injection have been reported by Lehman and Debbas.[8]

There has been a paucity of side-effects encountered in this study. A transient slight increase in heart rate and the sensation of flushing frequently occurred. These phenomena are generally encountered in angiographic studies.[19] The occurrence of a decreased amplitude of the QRS complex in the electrocardiogram of the patient with Ebstein's anomaly may not have been due to the particular contrast medium used. The increased susceptibility of patients with Ebstein's anomaly toward the development of arrhythmias has been reported.[15,21,22]

The lack of nausea and vomiting in this series may well be due to the routine use of hydroxyzine hydrochloride. This drug was also employed during angiography using other contrast media and found to be extremely helpful in preventing nausea and vomiting.

In view of the many factors which influence the quality of cine-angiographic films, variations in the sharpness of detail are inevitable. In general, the satisfactory roentgenograms obtained in this study suggest that the mixture of diatrizoate sodium and diprotrizoate with its relatively low iodine content (40 per cent) does not result in any significant loss of roentgenographic quality. The evaluation of this quality is based primarily upon a comparison with 500 cases using diatrizoate sodium and methylglucamine (hypaque-M, 90 per cent). The lack of untoward reactions was also a feature of this contrast medium; however, the higher viscosity is a definite handicap when large amounts are necessary.[4,5,12]

It appears that the lower iodine content of the new mixture diatrizoate sodium and diprotrizoate is compensated for by the larger amount of medium that can be injected per unit of time.

Fourteen of the patients receiving the mixture diatrizoate sodium and diprotrizoate (ditriokon) also received injections of diatrizoate sodium and methylglucamine (hypaque-M, 90 per cent) during the study. No distinct differences were observed between the angiograms. The amount of transient flushing was similar.

CONCLUSIONS

A new contrast medium consisting of a mixture of diatrizoate sodium and diprotrizoate (ditriokon) has a relatively low viscosity which facilitates manual or mechanical injections for angiography. During selective right heart catheterization and retrograde aortography, no significant adverse reactions were attributable to this contrast medium even when multiple injections were made. A total of 384 injections were performed in 216 patients. The quality of cine-angiographic films obtained was satisfactory for diagnostic purposes.

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Forty-fifth Annual Meeting: Mark Hopkins Hotel, San Francisco, Calif., April 1–4, 1963.

EDITORIAL

THE SIXTY-THIRD ANNUAL MEETING OF THE AMERICAN ROENTGEN RAY SOCIETY

THE Sixty-third Annual Meeting of the American Roentgen Ray Society was again held at the Shoreham Hotel in beautiful Washington, D. C., from Tuesday, October 2 through Friday, October 5, 1962. President Traian Leucutia called the meeting to order and introduced the Honorable M. Trobrine, President of the Board of Commissioners of the District of Columbia, who in well chosen words welcomed the Society to our nation's capital.

President-Elect Earl E. Barth was then installed as President of this Society and Dr. Robert C. Pendergrass, Chairman of the Executive Council, awarded the President's Medal to him. Following this the traditional presentation of a symbolic gavel fashioned from a mastodon's tooth recovered from Alaskan glacial ice and a working gavel fashioned from memorabilia of Röntgen, Coolidge and Snook was made by President Leucutia.

The Inaugural Address by President Barth entitled "Radiology and the Changing Medical Scene," stressed the importance of keeping radiologic practice patient-oriented and described certain outside influences which might affect this aim unfavorably. Radiology is a branch of medicine and has contributed immeasurably to the advancement of medicine. It must never be so "scientific" and so involved in technical features, nor so institutionalized, that the patient ceases to be the main concern. In rendering competent radiologic service, the private and/or office practice of radiology is a significant factor; its demise would be distressing and certainly would render our specialty less attractive to qualified young trainees. The apparent declining prestige of the physician is merely a reflection of the increasing medical sophistication of our American patient public. Dr. Barth's scholarly and thought-provoking Inaugural Address is published in full in this issue of the JOURNAL.

The Scientific Session of the Society began immediately thereafter with the presentation of ten papers devoted to various aspects of the examination and treatment of lesions of the head and neck. The roentgenographic evaluation of the temporal bone has become increasingly important with the development of surgical procedures in this area and a number of papers pertained to this subject. Three of these were concerned with radiation therapy.

The programming of scientific papers in the morning, providing time for study of scientific and technical exhibits as well as attendance at the Instruction Courses, was again carried out with considerable success this year. The scientific exhibits, so efficiently gathered and arranged by the Committee under the Chairmanship of Dr. James P. Cooney of New York City are described elsewhere in this issue of the JOURNAL.

On Tuesday evening the Annual Caldwell Lecture was given by Dr. C. Allen Good, Head, Section of Diagnostic Roentgenology, Mayo Clinic and Professor of Radiology, Mayo Foundation Graduate School, University of Minnesota, Rochester, Minnesota. The title of his lecture was "Tumors of the Small Intestine." Dr. Good was introduced by Dr. Clyde A. Stevenson, Director of Radiology, Sacred Heart Hospital, Spokane, Washington. Dr. Good, with characteristic thoroughness and ex-

traordinary clarity, presented the subject of tumors of the small intestine in a most interesting fashion. Based on one of the most extensive experiences to date, he well documented the relative incidence of these lesions and explored their numerous diagnostic implications. The overflowing audience was an expression of the great popularity of Dr. Good as well as of the high esteem in which he is held. Following Dr. Good's Lecture, President Barth presented to him the Caldwell Medal which is the highest award offered by the Society for meritorious and scientific achievement.

On Wednesday the Scientific Session was resumed with Dr. Richard Schatzki presiding. Nine papers on the diagnostic aspects of gastrointestinal tract conditions, a paper on the roentgen manifestations of hypokalemia, and a paper on radiation therapy with high energy electron beams employing pencil beam scanning were presented. Portable radioactive sources for diagnostic radiography and studies on oncolysis-promoting humoral substances produced by whole body irradiation were other subjects concluding the morning's presentations.

On Wednesday afternoon the activities of the American College of Radiology regarding its efforts to strengthen radiology and to better serve patients were lucidly described. Dr. Earl E. Barth was the presiding officer. Dr. Arthur J. Present moderated a panel on which Dr. T. J. Wachowski, Dr. George Cooper, Jr., Dr. Wallace D. Buchanan, Dr. John D. Reeves and Dr. A. Alan Sampson served. This informative panel presentation of the activities of the American College of Radiology was very well attended and delved into many extremely important problems which must be met and solved by this organization.

On Thursday morning scientific papers concerned with the study of speech, pulmonary arterial coarctations, angiography of the systemic pulmonary circulation, diagnosis of complications of cystic fibrosis, certain aspects of mammography, the effect of radiation on the physiology of small blood vessels, lymphatic dynamics in certain abnormal states, analysis of in-phantom dosimetry and an approach to radiation dosimetry in diagnostic radiology were presented. For this session an excellent symposium on "The Role of the Radiologist in Fallout Problems" was arranged by Dr. James P. Cooney who also acted as the Moderator. Colonel James T. Brennan discussed the various kinds of radiation injury produced by fallout and Dr. Lauriston S. Taylor dealt with certain aspects of the nuclear attack. A question and answer period relative to these problems ably conducted by Colonel James B. Hartgering concluded this extremely interesting and instructive symposium.

On Thursday evening the Annual Banquet was held in the Terrace Banquet Room with the announcement of the newly elected officers by Dr. Earl E. Barth. Awards were presented for scientific exhibits judged to be outstanding. Later, a most entertaining floor show was followed by a pleasant evening of dancing.

On Friday morning papers on a technique for renal cyst puncture, xanthomatous pyelonephritis, certain roentgen signs for severe hydronephrosis, evaluation of nephrotomography in urologic diagnosis, selective renal angiography, percutaneous left brachial aortography, and cinefluorographic investigation of the genitourinary tract were presented. Other papers dealt with intraosseous venography in pelvic malignancy, lymphangiography, cancer of the uterine fundus, carcinoma of the ovary and an after-loading cesium applicator for carcinoma of the cervix.

The dean of the Instruction Courses, Dr. Harold O. Peterson, assisted by Dr. Donn G. Mosser, again assembled a most interesting collection of courses on various aspects of radiology dealing with diagnosis, therapy and interrelated subjects. The attendance at these Instruction Courses is always a tribute to the judgment and organizational ability of Dr. Peterson and his associate.

The number of technical exhibits was the

largest of any meeting thus far held in Washington. These were assembled under the capable direction of Mr. Clifford L. Sherratt, Honorary Member, and Dr. James C. Cook, Manager of the Annual Meeting. A list of the technical exhibits is published elsewhere in this issue of the JOURNAL.

The location of the meeting in our nation's capital, beautifully architectured by the famous Charles Pierre L'Enfant, is always most satisfactory to members and guests of the Society. The Committee on Local Arrangements under the Chairmanship of Dr. Edgar M. McPeak, and the Ladies Committee under the most capable Chairmanship of Mrs. McPeak, afforded everyone an opportunity to enjoy various sights and sounds of Washington. On Monday, the ladies attended a golf widows' dinner at a famous seafood restaurant followed by a night bus tour of Washington. On Tuesday, Embassy tours and teas were arranged. A White House tour on Wednesday morning made it possible for the ladies to see the results of the First Lady's redecoration of portions of the White House and to admire priceless objets d'art—reminders of our early American heritage. A delightful luncheon followed at the Shoreham with a most entertaining presentation of human-like bunnies from "Hoppersville." A general tour of the Washington area, including Arlington and Mount Vernon with a luncheon in Arlington was slightly dampened by weather but nonetheless enjoyed by all on Thursday.

The Society is deeply indebted to Mrs. Edgar McPeak and her Committee for this outstanding program which delighted the ladies.

The Annual Golf Tournament, held at the Manor Country Club Monday afternoon and arranged under the Chairmanship of Dr. Ralph M. Caulk, again proved to be most enjoyable. This beautiful and difficult course afforded the golfers an opportunity to test their mettle and subsequently to attend an excellent golf dinner.

To the Management and Staff of the Shoreham Hotel, the Society extends its sincere thanks for excellent service. The many occasions on which the Society has returned to this hotel testifies to its popularity.

The Committee on Press Relations with Dr. Karl C. Corley as Chairman and with the aid and advice of Mr. Otha W. Linton and Mr. David G. Pettengill from the American College of Radiology released press notices and conducted various public relations activities.

Dr. Edgar McPeak deserves a special thank you for his suave, distinguished Chairmanship of the Committee on Local Arrangements.

President Barth may reflect in the glory of the largest attendance ever recorded at a meeting of the American Roentgen Ray Society. The meeting was conducted in a most congenial atmosphere and through this atmosphere the personality of its President shone most brightly.

KENNETH L. KRABBENHOFT, M.D.

THE SCIENTIFIC EXHIBITS

THE SCIENTIFIC EXHIBITS of the Sixty-third Annual Meeting of the American Roentgen Ray Society held at the Shoreham Hotel, Washington, D. C., October 2 to October 5, 1962 were the largest in number and volume in the Society's history and they were unquestionably of the highest technical quality and greatest documentary value. To Dr. James P. Cooney, enthusiastic and untiring Chairman of the Scientific Exhibits Committee who assembled this magnificent array of displays, thereby contributing immeasurably to the success of this year's Annual Meeting, the Society is greatly indebted and expresses its unbounded gratitude. The Committee on Awards must have had considerable difficulty in making the appropriate selection for the customary prizes. After thoughtful consideration, a Gold Medal, Silver Medal, Bronze Medal and 7 Certificates of Merit were awarded.

Gold Medal

A Dynamic Classification of Bone Dysplasias. Philip Rubin, M.D., University of Rochester Medical Center, Rochester, New York.

There is a logic to the order of bone growth. This order is the basis of the proposed dynamic classification of bone dysplasias by the exhibitor and rests on an understanding of the processes involved in normal bone development. All modeling errors are expressed as departures from the normal. The pathologic process in skeletal dysplasias is therefore due to deficiency or excess of a normal activity; *i.e.*, hypoplastic versus hyperplastic. The error is an intrinsic defect and is generalized in distribution. The selection of skeletal sites rests as much on the dynamics of bone modeling in different parts of the body as it does on the pathologic upset.

From the experimental induction of bone dysplasias by irradiation of selective sites, the exhibitor found that each specific segment of tubular bones has a specific function in modeling. If a certain process is altered, a specific abnormality results. The fundamental assumption of this classification is that there can be only one dysplasia for each error and conversely a specific error can result in only one dysplasia. There may be variations in presentation of the same dysplasia but the fundamental theme must be the same.

The exhibitor postulates certain sets of assumptions to evolve his hypothesis of bone modeling on the basis of experimental and clinical observations. These assumptions were listed in detail.

The following new terminology and classification are proposed:

DYSPLASIA. This is a disturbance in bone form or modeling which assumes a disturbance in growth, intrinsic to bone. The hypoplastic group comprises: *epiphysis:* Morquio's disease, epiphyseal dysgenesis punctata, epiphyseal dysgenesis multiforme; *physis:* achondroplasia, metaphyseal dysostosis; *metaphysis:* hypophosphatasia, osteopetrosis, metaphyseal dysplasia; *diaphysis:* osteogenesis imperfecta. The hyperplastic group includes: *physis:* Marfan's and Ollier's disease; *metaphysis:* exostosis; *diaphysis:* Engelmann's disease and hyperphosphatasia.

DYSTROPHY. This is a disturbance in bone form or modeling which assumes a disturbance in nutrition or metabolism extrinsic to bone. The conditions enumerated under this terminology are: *epiphysis:* hypothyroidism; *physis:* hypo- and hyperpituitarism, Hurler's syndrome; *metaphysis:* rachitiform diseases, Gaucher's disease, heavy metal intoxication, hypreparathyroidism; *diaphysis:* vitamin A and D intoxication.

DYSOSTOSIS. This is a disturbance in bone form or modeling which assumes a disturbance or defect in development or mesenchymal tissues. Under this classification are included: *epiphysis:* dysplasia epiphysealis hemimelica; *physis:* Ellis Van Creveld's syndrome, peripheral dysostosis; *metaphysis:* osteopoikilosis, osteopathia

striata, cortical defects; *diaphysis:* melorrheostosis, polyostotic fibrous dysplasia, cleido-cranial dysostosis.

Many beautiful roentgenographic reproductions and appropriate diagrams, skillfully displayed, illustrated this outstanding exhibit.

SILVER MEDAL

Some New Portable Radioactive Sources for Diagnostic Radiography. Kenneth L. Krabbenhoft, M.D., Harper Hospital, and Farno L. Green, M.S., Detroit, Michigan.

Radioactive isotope sources permitting portable applications in diagnostic radiography have been evaluated in the past. Such sources have displayed certain disadvantages. In the present investigation 4 isotopes were studied in relation to practicability of clinical application. The advantages of some of these radioisotope sources are as follows: easily portable; easily used; source cannot fail unexpectedly; constant voltage; electrical power not required; no electrical or explosion hazards; minimum system maintenance; operator easily protected; exposure times not critical with wide film latitude; low patient dosage; minimum space requirement for use and storage.

Radioactive isotopes emitting low energy photons (characteristic x-rays, gamma rays, Bremsstrahlung) suitable for clinical radiography are few in number. Certain factors such as problems of source fabrication, housing in a suitable exposure device, specific activity, necessary source size and useful life limit their scope. The disadvantages may be enumerated as follows: long exposure times; periodic source replacement is necessary; several isotopes with different energies are required to equal the versatility of x-ray; portable device containing the shielded source must be protected from loss.

Four radioisotopes were evaluated in clinical applications and compared with thulium 170 (Tm^{170}) which has been the subject of several previous studies during the past 12 years. These isotopes were: ytterbium 169 (Yb^{169}), gadolinium 153 (Gd^{153}), samarium 153 (Sm^{153}), and lutetium 177 (Lu^{177}). Their physical characteristics (approximate half-life, photon energies, source strength, pellet size, etc.) were presented in detail and compared with those of Tm^{170} and Co^{60}.

Yb^{169} (32 day half-life) was compared with Gd^{153} (240 day half-life) and Tm^{170} (127 day half-life) for relatively thin section radiography, *e.g.*, the hand. In the examination of thicker body sections, *e.g.*, the chest, Yb^{169} was compared with Sm^{153} (2 day half-life) and Lu^{177} (7 day half-life). The long half-life of Gd^{153} would suggest its preferability, providing sufficient source strength were available. Sm^{153} has an almost identical spectral energy distribution with Gd^{153} and therefore the results obtained with either of these radioactive isotopes would be comparable to the other in regard to quality, contrast, definition, etc.

Exposure times of less than 1 second were achieved with Yb^{169} sources in the radiography of extremities. Some Yb^{169} sources allowed chest exposures as short as 1 second. Exposures with other sources were considerably longer.

Further studies were made with stationary and reciprocating grids, variable exposure times and different source-film distances.

Of the sources investigated, Yb^{169} was found to be the most versatile because of adequate intensity, acceptable useful life, and wide energy spectral distribution. A portable unit which weighs only 25 pounds was constructed.

The practical application of this unit was illustrated by beautiful color photographs, and many unusual radiographs of good diagnostic quality were presented.

In the conclusion it was emphasized that radioisotope radiography is not competing directly with conventional roentgenographic techniques. The limitations are primarily the result of presently available specific activities. Remote areas and disaster situations where electricity is unavail-

able may be the most logical spheres for utilization of these portable units.

Bronze Medal

Normal and Pathologic Roentgen Anatomy of the Middle Ear and Mastoid Process. Lewis E. Etter, M.D., and Lawrence Cross, R.T., Western Psychiatric Institute and The Falk Clinic, Pittsburgh, Pennsylvania.

Conventional and magnification studies of the temporal bones of living subjects have been made to clearly demonstrate the anatomic features involved in the middle ear and its related parts.

Magnification of the anatomic structures has greatly helped in understanding relations of the internal acoustic meatus, cochlea, labyrinth, middle ear, attic, bony bridge, aditus, mastoid antrum and ossicles.

This excellent exhibit placed emphasis on precision roentgenography for either conventional or magnification techniques in order to delineate normal and pathologic processes. Variations of the dorsoventral angle were illustrated as well as angulations necessary to demonstrate the tympanic cavity and ossicles in the base view of normal subjects and in pathologic conditions.

Certificates of Merit

1. *Lymphography.* Patrick A. Dolan, M.D., University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

Lymphography provides a direct method of opacifying certain areas of the lymphatic system and has proved to be of great value in the investigation of patients with suspected or confirmed malignancy.

The technique of examination as perfected at the University of Texas M. D. Anderson Hospital and Tumor Institute was shown and experience with the first 200 cases was discussed. As would be expected in a tumor institute, there has been a very high incidence of pathology, a diversity of material and excellent clinical and pathologic correlation.

2. *Mammography.* Robert L. Egan, M.D., The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

The technique of soft tissue roentgenography of the breast was discussed as well as the amount of radiation received by the patient.

The study was based upon preoperative diagnosis of the surgeon, an independent evaluation by the radiologist and a final diagnosis of the pathologist. A total of 2,000 cases coming for biopsy were studied by 24 participating institutions in collaboration with the Cancer Control Program, U.S.P.H. Service. All mammograms were reviewed by the exhibitor as a blind study and all tissue sections were reviewed by a single pathologist.

Eight groups of mammograms were circulated for interpretation of the 24 participating institutions without other information.

Some additional 30 radiologists who have visited the M. D. Anderson Hospital and Tumor Institute for studying mammography and who have set up the technique in their respective institutions contributed their results. The exhibitor's own results as well as the composite results of the participating radiologists were presented in a statistical form. The importance of discovery of "occult carcinomas" was emphasized.

3. *Rheumatoid Arthritis; New Signs in Neglected Sites: The Shoulder Girdle and Thoracic Cage.* Frieda Feldman, M.D., and Meyer Alpert, M.D., Columbia Presbyterian Medical Center, New York, New York.

Both uncommon and hitherto undescribed roentgen manifestations as they affect the shoulder girdle and thoracic cage were illustrated and discussed. Although infrequently studied, these areas may be highly rewarding in the diagnosis of this disease.

4. *Roentgenologic Features of Single and Multiple Coarctations of the Pulmonary Artery and Branches.* Brit B. Gay, Jr.,

M.D., Wade H. Shuford, M.D., Robert H. Franch, M.D., and James V. Rogers, Jr., M.D., Emory University School of Medicine, Atlanta, Georgia.

The literature on coarctations of the pulmonary artery was reviewed. A series of 12 new cases was also presented, 2 with complete autopsy studies. The essential clinical features and cardiac catheterization findings were described.

The exhibit illustrated the roentgenographic and angiocardiographic features of the various types of pulmonary coarctation. An anatomic classification of the types was given.

Pulmonary artery coarctation is no longer considered a rare anomaly. With increasing knowledge of this condition, the number of cases diagnosed will probably rapidly increase.

5. *Certain Ring Shadows in the Stomach and Duodenum—Their Interpretation and Significance.* Mortimer Lubert, M.D., and George R. Krause, M.D., Mount Sinai Hospital, Cleveland, Ohio.

One generally overlooked cause of "ring shadows" is the ordinary peptic ulcer. In some instances, the ring shadow is the first or only way in which an ulcer may be seen. In other situations, the ring shadows may be the only way to confirm an ulcer seen in only one projection. When more than one ulcer is present, one may show as a fleck but the other is seen as a ring. The nature of the ring may be useful in the differential diagnosis between benign ulcer and carcinoma.

Clinical material, roentgenograms, and diagrams illustrating these points were presented.

6. *Plesiosectional Tomography of the Temporal Bone; A New Multi-Screen Cassette.* Margaret J. McGann, A.B., R.T., and Marc S. Lapayowker, M.D., Temple University Medical Center, Philadelphia, Pennsylvania.

A new multi-screen cassette was shown, enabling plesiosectional roentgenography with only 1 mm. separation between the layers, using conventional tomographic equipment and a single exposure.

The exhibit contained examples of temporal bone tomograms, beautifully illustrating the normal anatomy and selected pathologic conditions.

7. *Simple Radiographic Demonstration of Eustachian Tubes and Abnormalities.* M. H. Wittenborg, M.D., and E. B. D. Neuhauser, M.D., Children's Hospital Medical Center, Harvard Medical School, Boston, Massachusetts.

A simple new technique for radiography visualizing patency, non-patency and abnormalities of the eustachian tube was presented and some of the abnormalities were demonstrated.

The study extended from the newborn to the adult, and the exhibit contained numerous splendid examples illustrating the diagnostic value of the technique.

Other Exhibits

Other excellent exhibits were:

Laminagraphic Control for Stereotactic Thalamotomy. Colvin H. Agnew, M.D., Karl Youngstrom, M.D., and Charles Brackett, M.D., University of Kansas Medical Center, Kansas City, Kansas.

This exhibit demonstrated the technique permitting precise localization of the anterior and posterior commissure with air contrast. Coordinates of the thalamic nuclei are determined from the anterior commissure. The stereotactic device enables introduction of the balloon-type pallidotomy needle with minimum undesirable damage.

The method of precise localization supplements the clinicopathologic studies augmenting present knowledge. The preliminary results obtained in Parkinson's disease were tabulated.

Roentgenkymography of the Heart. Gilbert H. Alexander, M.D., and Marie H. Manno, M.D., St. Francis General Hospital and Rehabilitation Institute, Pittsburgh, Pennsylvania.

Kymographic studies of the heart were evaluated to determine criteria offering reliable information in regard to the specific diagnostic problem. Examples of proven

cases of acquired and congenital heart disease were presented.

Organ Scanning With Radioactive Isotopes; Examples of Clinically Useful Scans. Harold L. Atkins, M.D., Columbia-Presbyterian Medical Center, New York, New York.

Clinically useful scans performed with various isotopes were demonstrated. Cold and hot thyroid nodules, substernal goiter and thyroid carcinoma were seen with I^{131}. Splenic localization with Cr^{51}, kidney localization with Hg^{203} and liver scans with Au^{198} demonstrated a variety of clinical conditions.

Malformation of Intracranial Vessels; Surgical Treatment With Artificial Emboli. Willy E. Baensch, M.D., and Alfred B. Luessenhop, M.D., Georgetown University Medical Center, Washington, D. C.

The exhibitors found in their vast material of cerebral arteriograms quite a number of malformations, which may cause severe headache, hemorrhages, epilepsy and heart disease. As the multiplicity of the aneurysm is well known, they concentrated on arteriovenous fistula, which is, unfortunately, called in many monographs "aneurysm," although in fact, it is a short-circuit between an artery and a vein. Since the involved veins are markedly dilated, surgical treatment is being tried.

Luessenhop and Fulcher treated such cases very successfully with an artificial embolus. Arteriograms before and after surgical treatment were shown.

Gravitational Placentography. Frank Behlke, M.D., Harry W. Fischer, M.D., and William C. Goddard, M.D., College of Medicine, State University of Iowa, Iowa City, Iowa.

Gravitational placentography, a method of indirectly localizing the placenta, based on the effect of gravity on the fetus in relation to the maternal pelvis was utilized in a two-year period at the University of Iowa Hospital. With the "double set-up" examination performed by the obstetrician, as indicated, the combined roentgenologic and clinical accuracy was high. Advantages in addition to the accuracy, are that no special equipment or injection procedure is required and radiation exposure is not excessive. In each case, this cooperative approach led to correct handling of the bleeding third trimester patient.

The exhibit demonstrated the method in detail.

Demonstration of Calcified Coronary Arteries in Humans Using Image Amplification Fluoroscopy. Charles E. Bickham, Jr., M.D., and Carolyn Edwards, M.D., Doctors Hospital, Washington, D. C.

This exhibit contained roentgenograms of postmortem hearts demonstrating the types of coronary artery calcifications. Also injected hearts were demonstrated. A number of roentgenograms of the chest and spot films showed the calcified coronary vessels which were seen during fluoroscopy.

The panels included in the exhibit illustrated the technique, limitations, other techniques available, the differential diagnosis, and the clinical value of the examination.

Medical Photoscanning Utilizing Closed Circuit Television. Prentiss M. Dettman, M.D., Ronald R. Lund, M.D., and Loy T. Brown, M.D., U. S. Naval Hospital, National Naval Medical Center, Bethesda, Maryland.

A brief introduction to radioisotope organ photoscanning was presented with representative examples of thyroid, liver, kidney, brain, spleen, heart and bone scans displayed.

A continuous silent movie was projected through a simulated television screen to show the application of television contrast enhancement.

Roentgenographically Controlled Percutaneous Injection Through the Foramen Ovale of the Trigeminal Root for Tic Douloureux and of the Thalamus for Parkinsonism. Arthur Ecker, M.D., and Theodore Perl, M.D., State University of New York College of Medicine, Syracuse, New York.

This exhibit consisted of a series of photographs, drawings, and roentgenograms illustrating two techniques.

The first is a method of placing a needle accurately in the trigeminal ganglion for alcohol injection in the treatment of tic douloureux. Preliminary roentgenograms are made for the guidance of insertion of the needle through the cheek and foramen ovale, and roentgenograms with the needle in place are made for precise adjustment of depth.

The second technique is an extension of the first. It permits accurate placement of a needle through the cheek and foramen ovale into the antero-infero-lateral portion of the thalamus for thalamolysis in the treatment of the rigidity and tremor of parkinsonism. Roentgenograms are made to determine the target in the thalamus and the entry point on the skin in relation to the foramen ovale.

New Technique for Accurately Projecting the Dorsum Sellae into the Foramen Magnum. Lewis E. Etter, M.D., and Lawrence Cross, R.T., Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania.

This new technique was described in detail and the appropriate projection angle was illustrated on dry skull specimen.

Percutaneous Transhepatic Cholangiography. John A. Evans, M.D., Peter Tillotson, M.D., and Zuheir Mujahed, M.D., The New York Hospital—Cornell Medical Center, New York, New York.

The differentiation between obstructive and hepatocellular jaundice remains difficult and sometimes impossible despite the best clinical and laboratory knowledge. Conventional diagnostic roentgen examinations of the gallbladder and bile ducts offer no help since oral and intravenous cholangiography are of no value in the presence of jaundice and high serum bilirubin. Percutaneous transhepatic cholangiography provides the opporutnity of visualizing the bile duct system when oral or intravenous methods fail. It is particularly helpful in the presence of clinical or chemical jaundice and offers the opportunity of diagnosis prior to surgical exploration. It is, furthermore, capable of demonstrating intrahepatic pathology not identifiable by other known preoperative or operative diagnostic methods.

This exhibit demonstrated that percutaneous transhepatic cholangiography provides definitive diagnostic information in situations which otherwise might require exploratory laparotomy for recognition of the problem.

The Radioactive I^{131} Rose Bengal Hepatoscan. Frieda Feldman, M.D., Sidney Rubenfeld, M.D., and Carl Collica, B.S., Department of Radiation Therapy, New York University, Bellevue Medical School, New York, New York.

The radioisotopic survey technique as applied to hepatoscanning with I^{131} rose bengal furnishes a simultaneous functional and anatomic approach to the diagnosis of hepatic diseases.

An accurate liver function test facilitates detection of focal or diffuse hepatic abnormalities, isolates and pinpoints disease. Accurate localization of the lesion yields superior diagnostic results in conjunction with clinical evaluation, biochemical study and needle biopsy. The combined approach is superior to any single technique used alone. Maximum information is obtained.

The method establishes diagnostic patterns in a variety of clinical situations.

The exhibit presented the method, material and results in detail.

Roentgenologic Observation of Growth Rates of Colonic Polyps and Cancer. Leo S. Figiel, M.D., Steven J. Figiel, M.D., and Fred K. Wietersen, M.D., Grace Hospital, Detroit, Michigan.

A series of cases illustrating the development of cancer of the colon in typical advanced forms was presented. Correlation of time and growth was made and a growth cycle or "doubling time" was established for each case. Roentgenographic differentiation of benign and malignant polyps was discussed and illustrated. Criteria for surgery of colonic polyps were given.

Hyperplastic Cholecystoses. John P. Fotopoulos, M.D., Arthur R. Crampton, M.D.,

and Howard C. Burkhead, M.D., Evanston Hospital (Northwestern University Medical School), Evanston, Illinois.

Hyperplastic cholecystosis is a complex of non-inflammatory, non-calculous gallbladder diseases which includes cholesterolosis, adenomyomatosis and associated neuromatosis. In certain individuals this abnormality is clinically significant.

The various roentgen manifestations of cholesterolosis and adenomyomatosis were illustrated. Gross and microscopic material from selected operated cases was shown.

Lymphangiography in Therapy and Surgery. Col. H. C. Harrell, MC, Chief, Capt. R. M. Wright, MC, Capt, F. A. Halaby, MC, Capt. J. H. Freeman, MC, Capt. J. C. Turner, MC, and Capt. L. Galdieri, MC., Radiology Service, Walter Reed General Hospital, Washington, D. C.

This exhibit demonstrated the use of lymphangiography in pre- and post-lymphadenectomies as an aid to lymph node dissection at the time of surgery, and for postsurgical evaluation of the effectiveness of the dissection. A lymphangiographic demonstration of post-lymphadenectomy complications was included.

Another section showed the method and value of utilizing opacified lymph nodes for following the results of radiation therapy and in detecting subsequent metastatic lesions.

Also included was a section dealing with the possible therapeutic applications of lymphangiography, through the utilization of intralymphatic injections of radioisotopes.

A Case of the Day. Col. H. C. Harrell, MC, Chief. Presented by Capt. J. H. Freeman, MC, Radiology Service, Walter Reed General Hospital, Washington, D. C.

In this exhibit an interesting "case of the day" was presented with all pertinent data for the diagnostic acumen of the visiting participants.

Neonatal Intestinal Obstruction. John W. Hope, M.D., Milton L. Wagner, M.D., and Klaus W. Bren, M.D., The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

Intestinal obstruction in the newborn is a surgical emergency. Its prompt recognition by the clinician and diagnosis by the radiologist can be lifesaving.

This exhibit was designed to illustrate the more commonly encountered lesions from the pylorus to the anus. Particular attention was directed to the usefulness of air rather than an opaque contrast medium to establish a diagnosis.

Left Brachial Aortography. Bill G. Karras, M.D., and Abram H. Cannon, M.D., Department of Diagnostic Radiology, Chicago Wesley Memorial Hospital and Northwestern University Medical School, Chicago, Illinois.

This exhibit demonstrated the technique and results of a new method of aortography. By means of a pressure injection of the contrast medium into the left brachial artery through a No. 17 gauge needle excellent visualization of the abdominal aorta and its vessels is obtained. No catheter cut-down or direct aortic puncture is needed.

The technique, examples of aortograms and the advantages of the method were described in detail.

Ego-D-Flater III. Elliott C. Lasser, M.D., John H. Feist, M.D., Robert N. Berk, M.D., and Richard C. Granke, B.S., University of Pittsburgh School of Medicine, Presbyterian-University Hospital, Pittsburgh, Pennsylvania.

An automatic testing and grading device illustrating the possibility of errors in roentgen diagnosis based on gross morphology alone was presented. Two anatomic regions were utilized, *i.e.*, the descending duodenum and the breast.

Roentgen Demonstration of Lesions of the Hypopharynx. J. Francis Mahoney, M.D., and Thomas C. Jacob, M.D., Fitzgerald Mercy Hospital, Darby, Pennsylvania.

This exhibit was a demonstration of the anatomy, function and lesions found in the hypopharynx. Spot filming technique was used with barium double contrast roent-

genograms obtained during fluoroscopic observation. Cases demonstrating tumors, the regression of tumors during radiation therapy, anomalies, pneumatoceles, post-operative appearance after radical surgery and cases showing a neurologic deficit were presented.

Increased Radiosensitivity Through Intra-Arterial Infusion of Hydrogen Peroxide. John T. Mallams, M.D., George A. Balla, M.D., and James W. Finney, M.A., Baylor University Medical Center, Dallas, Texas.

There is evidence to support the hypothesis that a direct relationship exists between available oxygen and tissue radiosensitivity. Various investigators accepting this thesis have shown that by increasing the available oxygen in human tumors, radiosensitivity is thereby increased. Studies in humans and animals in whom hydrogen peroxide was used as a source of oxygen in a regional intra-arterial infusion system were discussed.

Photographs of the procedure, animals and humans were shown, illustrating the efficacy of this method.

Multiple telephones were provided for listening to the tape recorded protocols.

Evaluation of a New Angiographic Contrast Medium. T. R. Marshall, M.D., and T. Ling, M.D., Department of Radiology, University of Louisville School of Medicine, Louisville, Kentucky.

This exhibit gave a brief summary of the development of the opaque media. Some advantages of a new opaque medium were also discussed.

The clinical evaluation in over 1,000 patients and 1,925 injections was presented.

Opacification of Small Bowel with Intravenously Administered Contrast Medium. James T. McClintock, M.D., and Emanuel Salzman, M.D., Denver General Hospital, Denver, Colorado.

The purpose of this exhibit was to describe the technique and mechanism of opacifying the small bowel in the experimental animal with the use of an intravenously administered contrast medium.

In the cat, the urinary tract visualized following intravenous injection of sodium diatrizoate 0.1 gm./kg. Progressive increase of this dose to 1 gm./kg. resulted in the visualization of the gallbladder and at still higher dose levels in visualization of the small bowel, in addition to the urinary tract.

It appears that the contrast medium is actively secreted by the epithelium of the small bowel into the lumen where it is propelled by peristalsis into the colon.

The exhibit illustrated the potential application of this technique in evaluating functional and morphologic changes in the human small bowel, particularly, the diagnosis of mesenteric vascular occlusions.

Roentgen Manifestations of Myeloma. William T. Meszaros, M.D., Joseph J. Litschgi, M.D., Hildegarde Schorsch, M.D., and Franz Gampl, M.D., Cook County Hospital, Chicago, Illinois.

Myeloma has many atypical manifestations. The exhibit demonstrated the following: cyst-like, solitary, extra-large, moth-eaten, sclerotic, osteoporotic and phalangeal extra-medullary changes; amyloidosis; long-term progress; and myeloma simulating tuberculous spondylitis.

Correlative Cholangiographic Anatomy. Frank Moody, M.D., Thane Asch, M.D., John A. Evans, M.D., and Frank Glenn, M.D., New York Hospital—Cornell Medical Center, New York, New York.

The normal and morbid intrahepatic anatomy of the human biliary tree was displayed by comparing postmortem cholangiograms with their vinyl acetate cast representation. The value of lateral cholangiography was demonstrated. Changes which accompany intrahepatic and extrahepatic observation as well as metastatic tumors were shown.

Histoplasmosis—Variability of the Roentgenographic Pattern; An Analysis of 200 Cases. Joseph W. Peabody, Jr., M.D., Sol Katz, M.D., William S. Lyons, M.D., and Edgar W. Davis, M.D., Georgetown University School of Medicine, Washington Hospital Center and VA Hospital, Washington, D. C.

This exhibit illustrated the extreme variability of the roentgenographic appear-

ance of pulmonary histoplasmosis. It was based on an experience with 200 personal cases of proved histoplasmic infection, from which it has become apparent that it is (1) an extremely important clinical entity, (2) frequently misdiagnosed, and (3) capable of mimicking any and all of the characteristics of tuberculosis.

Selected cases were shown, the roentgenograms being accompanied in most instances by gross and microscopic color photographs. Sixteen different categories were included and each, in addition to being documented roentgenographically, was illustrated by a drawing that should clarify its appearance for every observer.

Besides showing the manifestations of histoplasmosis as an acute or chronic infection, the exhibit contained many examples of the severe and startling problems that may result unexpectedly from healed histoplasmosis. These comprised broncholithiasis, bronchial obstruction, massive hemoptysis, bronchiectasis, superior vena caval syndrome, esophageal compression and esophagobronchial fistula. Instances of each were shown.

Renal Cyst Puncture (The Technique of). Harold O. Peterson, M.D., and John A. Tobin, M.D., University of Minnesota Hospitals, Minneapolis, Minnesota.

Differentiation of a benign renal cyst from a solid renal neoplasm cannot always be made on the basis of plain roentgenograms or urographic studies.

This procedure entails the introduction of a styleted needle, percutaneously, into the suspected cyst. Fluoroscopic control is used after prior cyst localization by plain roentgenograms and pyelograms. After entering the cyst and aspirating some of its contents, contrast material is injected and roentgenograms made in several projections. The diagnosis is made from the contour and shape of the lesion. The procedure has been used for several years without major complications.

The technique was presented in detail.

A New Technique for the Roentgen Examination of the Colon. Rubem Pochaczevsky, M.D., and Robert S. Sherman, M.D., Department of X-Ray Diagnosis, Memorial Hospital, Memorial Sloan-Kettering Center for Cancer & Allied Diseases, New York, New York.

A new method of double contrast examination of the colon was presented utilizing carbon dioxide as the gas and employing a closed system, one stage technique. A prepackaged, disposable barium enema kit and the careful selection of a barium mixture contribute in an important way to the success of the method.

Newer Techniques of Soft Tissue Roentgenography of the Breast. Kenneth L. Rall, M.D., Theodore E. Keats, M.D., George F. Koenig, R.T., and Darrell D. Wood, R.T., University of Missouri School of Medicine, Columbia, Missouri.

This exhibit presented a new technique for soft tissue roentgenography of the breast. The technique utilizes low kv. and low ma. which results in improved detail with diminution of patient radiation dosage and produces a mammogram of improved quality and contrast. The exhibitors' experience with magnification roentgenograms of the breast was also presented and illustrated with appropriate clinical material. The applicability of this technique to the small atrophic breast was stressed.

Pathologic Lesions of the Hip and Pelvis in Children. Capt. Charles A. Rockwood, Jr., M.D., and Hooshang Taybi, M.D., USAF Hospital Lackland, Lackland Air Force Base, Texas.

This exhibit contained a complete roentgenographic collection of the common and the uncommon pathologic lesions of the hip and pelvis which are seen in infants and children. Forty-two different conditions were presented along with a brief history and a diagnosis in each instance. The description of an additional 30 conditions, with a brief history and diagnosis, was available in booklet form at the exhibit.

Perigastric Adhesions. Charles E. Shopfner, M.D., St. Mary's Hospital, Grand Junction, Colorado.

Perigastric adhesions cause deformity of the stomach that can be confused with carcinoma. A review of 50 cases of perigas-

tric adhesions was presented with emphasis placed on the etiology, pathology and roentgen findings. A new roentgenographic sign was described, which is called the "trapped-air" sign. The principle of the sign and its diagnostic significance were discussed.

The sign has proven important and helpful in differentiating deformity caused by perigastric adhesions and carcinomas. The exhibitor feels that, when the sign is present, carcinoma is excluded.

Mammography: An Examination of Mammographic Techniques. W. E. Siler, M.S., R. Garrett, M.S., R. E. Snyder, M.D., J. S. Laughlin, Ph.D., and R. S. Sherman, M.D., Memorial Sloan-Kettering Cancer Center, New York, New York.

The physical parameters of mammography have been examined with the view of aiding the individual radiologist in the selection of the techniques best suited to his own situation.

This exhibit presented the results of that work in great detail.

The following suggestions are made for establishing a working mammographic technique: Kodak AA, Ansco Super-ray A, or equivalent film; target skin distance of 24 inches; mas. fixed, 600 to 1,200 depending on rating of tube and generator; base kv. established by trial and error to deliver a properly-exposed film for an average breast of known thickness, thereafter for each 1 cm. increase in thickness add 1 kv. or for each 1 cm. decrease in thickness subtract 1 kv., for very firm breasts, add 1 or 2 kv., for very fatty breasts, subtract 1 kv. By increasing development time from 5 to 10 minutes, mas. may be decreased by approximately 40 per cent for type M and 20 per cent for type AA film, with only a slight increase in fog level and a slight reduction in resolution.

What is a Normal Breast? (in Mammography). Philip Strax, M.D., and Maurice M. Pomeranz, M.D., City Hospital at Elmhurst, Elmhurst, New York.

The breast is a dynamic structure, strongly influenced by age, sexual development, glandular secretions, pregnancy and lactation. There are wide variations in size and structural elements as seen on soft tissue mammograms in apparently normal women.

This exhibit, based on a study of 2,000 women, was an attempt to classify the normal variations to serve as a guide for the determination of the abnormal.

Unusual Urologic Problems in Childhood. H. Taybi, M.D., M.S., and H. D. Riley, Jr., M.D., Children's Memorial Hospital, University of Oklahoma Medical Center, Oklahoma City, Oklahoma.

Urinary tract problems are frequently encountered in pediatric practice. In this exhibit some of the more infrequent urinary problems of infancy and childhood were demonstrated. The exhibit illustrated the value of voiding cystourethrograms in the detection of upper and lower urinary tract disorders. Rare conditions such as clear cell carcinoma of the kidney, sponge kidney, glycogen storage disease of the kidney, multilocular cysts of the kidney, "pine-tree" bladder in patient with pelvic fluid and edema, etc., were shown.

Selective Renal Angiography. Peter M. Tillotson, M.D., and Mordecai Halpern, M.D., The New York Hospital—Cornell Medical Center, New York, New York.

Selective renal angiography provides complete, precise, detailed visualization of the renal parenchyma and vascular bed. The technique, indications and results of applications of selective renal arteriography and phlebography were discussed. Examples of angiographic studies of renal cysts, malignant tumors, pyelonephritis, etc., were shown.

Wide Angle Roentgenography. Sol. M. Unger, M.D., Herbert S. Berlin, M.D., and Leon J. Corbin, M.D., Veterans Administration Hospital, Bronx, New York.

A new roentgenographic technique has been developed for illustrating peripheral lung lesions or abnormalities of the axillary portion of the thorax. Two conventional films at right angles to each other are mounted in an easily constructed frame

and with one exposure, two roentgenograms of excellent diagnostic quality are obtained. Its usefulness, not only in the thorax, but also in the area of the sacroiliac and hip joints was demonstrated.

Polytomography of the Ear. Galdino E. Valvassori, M.D., University of Chicago, Chicago, Illinois.

With the progressive improvement of laminagraphy, the normal and pathologic appearance of the external, middle and internal ear has become a problem of the radiologist, enhancing the field of surgical otolaryngology.

This exhibit presented a study of the normal roentgenographic anatomy of the ear as well as of a variety of pathologic conditions.

Special Exhibit

The People Who Work with X-Rays. American College of Radiology.

This was an educational exhibit prepared by the American College of Radiology as a public service.

The exhibit will be available to local radiological societies on loan for use at health fairs, career days, open house days, and speaking dates. Please write to the American College of Radiology, 20 North Wacker Drive, Chicago 6, Illinois.

THE TECHNICAL EXHIBITS

THE TECHNICAL EXHIBITS of the Sixty-third Annual Meeting of the American Roentgen Ray Society held at the Shoreham Hotel, Washington, D. C., October 2 to October 5, 1962 exceeded all previous records in Washington—by consensus the most favored meeting place of our Society. The rapid progress made in all branches of radiology, dependent on the many new advances in the devices of ultra-modern equipment for diagnostic and therapeutic purposes, has culminated in a dazzling array of apparatus which were displayed in a most artistic fashion. The continuation by President-Elect Earl E. Barth and his Program Committee of the policy of holding the Scientific Sessions in the morning afforded the members of the Society and their guests ample time to visit these splendid exhibits. This arrangement proved mutually rewarding to exhibitors and visitors. The tireless work of Mr. Clifford L. Sherratt, Honorary Member, and Dr. James C. Cook, Manager of the Annual Meeting, was an additional factor contributing to the outstanding success of the exhibits.

The Society expresses to all exhibiting firms its profound appreciation and extends its most sincere thanks.

The following is a list of the firms which participated in the Technical Exhibits:

Abbott Laboratories, North Chicago, Illinois; Albert-Acan X-Ray Solutions, Inc., Woodside, New York; Ansco, Binghamton, New York; Atomic Energy of Canada Limited, Ottawa, Ontario, Canada; Automatic Seriograph Corporation, College Park, Maryland; Barnes-Hind Barium Products Co., Sunnyvale, California; Bar-Ray Products, Inc., Brooklyn, New York; Bell-Craig, Inc., New York, New York; Cordis Corporation, Miami, Florida; Lester A. Dine Company, Floral Park, Long Island, New York; Di-Noc Chemical Arts, Inc., Subsidiary of Minnesota Mining & Manufacturing, Honeoye, New York; Dunlee Corporation, Bellwood, Illinois; E. I. du Pont de Nemours & Company, Inc., Wilmington, Delaware; Eastman Kodak Company, Rochester, New York; Eureka X-Ray Tube Corporation, Chicago, Illinois, E-Z-EM Company, Inc., Great Neck, Long Island, New York; Forsyth X-Ray Corporation, Chicago, Illinois; E. Fougera & Company, Inc., Hicksville, Long Island, New York; Franklin X-Ray Corporation, Philadelphia, Pennsylvania; General Electric Company, Milwaukee, Wisconsin; Gordon Consultants, New York, New York; Great Books of the Western World, Chicago, Illinois; Grune & Stratton, Inc., New York, New York; Halsey X-Ray Products, Inc., Brooklyn, New York; The Holter Company, Bridgeport, Pennsylvania; Howdon Videx Products Corporation, Mount Vernon, New York; Ilford, Inc., New York, New York; Keleket X-Ray Corporation, Waltham, Massachusetts; Leishman X-Ray Engineering Corporation, Los Angeles, California; Liebel-Flarsheim Company, Cincinnati, Ohio; Little, Brown & Company, Boston, Massachusetts; Low X-Ray Corporation, New York, New York; Machlett Laboratories, Inc., Springdale, Connecticut; Mallinckrodt Chemical Works, St. Louis, Missouri; Mattern Corporation, Chicago, Illinois; Micro X-Ray Recorder, Inc., Chicago, Illinois; North American Philips Company, Inc., New York, New York; Pako Corporation, Minneapolis, Minnesota; Pelvic Anchor Corporation, Rochester, New York; Pennsylvania X-Ray Corporation, Glenside, Pennsylvania; Physicians' Technical Equipment Company, Milwaukee, Wisconsin; Picker X-Ray Corporation, Cleveland, Ohio; Profex-ray, Inc., Maywood, Illinois; Purdue Frederick Company, New York, New York; W. B. Saunders Company, Philadelphia, Pennsylvania; Schick X-Ray Company, Inc., Chicago, Illinois; Frank Scholz X-Ray Corporation, Boston, Massachusetts; Sie-

mens New York, Inc., New York, New York; E. R. Squibb & Sons, New York, New York; Standard X-Ray Company, Chicago, Illinois; States Smelting & Refining Corporation, Lima, Ohio; Charles C Thomas, Publisher, Springfield, Illinois; United States Radium Corporation, Morristown, New Jersey; Westinghouse Electric Corporation, Pittsburgh, Pennsylvania; Williams & Wilkins Company, Baltimore, Maryland; Winthrop Laboratories, New York, New York; and Year Book Medical Publishers, Inc., Chicago, Illinois.

INTERNATIONAL COMMISSION ON RADIOLOGICAL UNITS AND MEASUREMENTS (ICRU)

REPORT TO THE INTERNATIONAL EXECUTIVE COMMITTEE
(TENTH INTERNATIONAL CONGRESS OF RADIOLOGY, 1962, MONTREAL, CANADA)

CURRENT PROGRAM

A TWO week meeting of the ICRU was held in Montreux, Switzerland, April 2nd to April 14th, 1962. This meeting included the Main Commission and all of the Committees that had reports prepared for final approval. Some 70 persons attended. An additional meeting of the Commission and Committee Officers was held in Ottawa from August 21 to August 23, 1962 for the principal purposes of the preparation of this report for the Tenth International Congress of Radiology and the outlining of program objectives for the next several years.

The 1956 report called attention to some basic problems in the establishment of radiation quantities and units. These were the subject of major discussions during and following the 1958 meetings. One of the difficulties is in reconciling the differences between radiation quantities and units as they have evolved over the past 30 years, and the system of quantities and units as used in the physical and engineering sciences. There are obvious divergencies between the two sets. It appeared possible that a complete resolution of this difficulty might necessitate abandonment of the quantities and units as used by the medical profession. This would accomplish a reconciliation between the two systems but it did not appear that it would introduce any substantial improvement in the understanding and utilization of the quantities by the medical profession. Naturally, there was considerable hesitancy about taking such a step.

As indicated in the 1959 report, an *ad hoc* committee was set up for the purpose of examining the whole problem of radiation and quantities and units. This committee has met three times (Munich, 1959; Geneva, 1960; Copenhagen, 1961). The study represented a moderate amount of compromise of viewpoints but it is believed that the final report now provides a consistent and satisfactory set of definitions for use in radiation measurements.

Several meetings of committees or committee task groups have been held during the past 3 years. A meeting of Committee III-B (Clinical Dosimetry) in Geneva in April 1961 was jointly sponsored and financed by the ICRU, WHO, and the IAEA. For this meeting, a number of additional consultants were invited to attend. Following the general meetings, a closed meeting of the committee membership was held for a period of 2 days to prepare a draft report.

In addition, there were meetings of various task groups of the committee on Standards and Measurement of Radiological Exposure—in Paris in January 1961 and in London in April and September 1961. The committee on Radiobiological Dosimetry held a meeting in April 1961. The ICRU was represented at a meeting of the International Bureau of Weights and Measures in Paris in October 1961.

As noted in the last report, two joint committees had been established between the ICRU and the ICRP. The Joint Committee on RBE has met twice with ICRU participation. The Committee on Methods and Instruments for Radiation Protection has not met.

Upon the request from the United Nations Scientific Committee on the Effects of Atomic Radiations, the ICRU and the ICRP agreed to undertake a second study dealing with the Medical and Physical Parameters in Clinical Dosimetry. This committee met in New York for one week in September 1959 and for a week in Stockholm in June 1960. A report of this study

entitled *Exposure of Man to Ionizing Radiation Arising from Medical Procedures with Special Reference to Radiation Induced Diseases; An Inquiry into Methods of Evaluation* was published in Physics in Medicine and Biology, 1961, Vol. *6*, No. 2, 199, Taylor and Francis, Ltd., London, England.

Reports and recommendations of the ICRU, originally designed for medical applications, have come into common use in other fields of science, particularly where "dosimetric" considerations are involved. For this reason, the committees have included in their membership some scientists having competence outside of the medical radiology field. Material in the reports is designed to meet physical, biological, and medical requirements wherever possible.

A question has been raised by the International Society of Radiology, regarding the possible formation of a new commission to study the characteristics of radiation equipment. Since this might overlap or coincide with the program of ICRU Committee IV established in 1956, the question was discussed at length by the ICRU. The following resolution resulted:

The ICRU considers that its responsibilities include the formulation and definition of methods of evaluation of radiological equipment. This activity results in recommendations of measurement techniques and performance criteria of radiological equipment, but excludes specific standardization of design even though it influences such designs. The work of the Committees of the ICRU has already progressed quite well along these lines and they have found valuable their close integral association within the ICRU.

The scope of activity and balance of medical and technical membership of the appropriate Committees are under review and deserve further modification and extension in directions as suggested by the International Society of Radiology. Specifically, in groups concerned with diagnostic and therapeutic problems it is planned that the Chairmanship and Vice-Chairmanship shall include a medical radiologist and a physicist or technical expert in radiological equipment.

It is therefore recommended that the work of the ICRU Committees be supported and strengthened and that it is unnecessary to establish a new Commission for this purpose.

It is of interest to note the widespread distribution of the membership of the commission and its committees. The following listing indicates the number of ICRU participants from the several countries:

U.S.A.	34
U.K.	30
Germany	21
France, Sweden	10 each
Netherlands, Canada	8 each
Belgium, Italy, Japan	3 each
Australia	2
Austria, Denmark, Poland, South Africa, Spain, USSR, Uruguay	1 each

The total number of participants is 139, from 18 countries. With one or two exceptions, this indicates a fairly satisfactory distribution.

Future Efforts

The ICRU is now planning the program it will undertake during the next several years. In this connection, the Commission's substructure and mode of operation have been reorganized in a way which, it is believed, will greatly facilitate its work. The new substructure will consist of *Planning Boards* and *Task Groups*.

The *Planning Boards* will be concerned with a continuing review of the various areas of activity determined to be of interest to the Commission. The *Task Groups* will be operating units charged with the responsibility of developing the necessary material for ICRU reports and studies.

In establishing this new substructure, the ICRU, of course, needs a fairly large roster of individuals on whom it can call for future tasks. To assist in compiling this roster, the Commission has decided to ask other organizations having an interest in radiological units and measurements for suggestions regarding individuals who might be willing to work with the ICRU.

THE CURRENT SERIES OF REPORTS

Hitherto, the triennial reports of the ICRU have been published in single volumes. However, the reports are now becoming too extensive, and in some cases too specialized, to make a single publication practicable. Beginning with the 1962 series, the ICRU reports will be issued in smaller entities, each dealing with a limited range of topics. This will make it possible to separate those recommendations expected to have validity for a long period of time from those that may need frequent revision.

The current report series include revision of much of the material that appeared in the 1959 report in addition to a number of new topics. The following summary indicates some of the highlights of the current report series:

Radiation Quantities and Units (Report 10a)—This report resulted from the thorough study by the *ad hoc* Committee on Quantities and Units mentioned above. It includes new names for certain quantities and clarified definitions for others. It presents a system of concepts and a set of definitions which is internally consistent and yet of sufficient generality to cover present requirements and such future requirements as can be foreseen.

Physical Aspects of Irradiation (Report 10b)—This report deals broadly with the physical aspects of irradiation with a considerable amount of new material developed since the 1959 report. It includes an extensive discussion of the various techniques for the measurement of absorbed dose as well as exposure. Characteristics of radiation instrumentation are covered in some detail including the more sophisticated work on standards. The section on spectra has been up-dated and a new section added on neutron measurements and standards. Available data for stopping power ratios and the average energy (W) required to produce an ion pair in a gas have been reviewed. On the basis of this review, it has been necessary to modify the previous ICRU tables for these factors. This modification amounts to about 1 or 2 per cent change in stopping power ratios and up to 1 per cent in W.

Radioactivity (Report 10c)—The portions of the report dealing with direct and relative measurements of radioactivity and the availability and requirements for radioactivity standards, and the parts dealing with the techniques and measurements of radioactivity in hospitals and biological laboratories supplement the 1959 report, embracing a review of the developments that have occurred since that report and bringing up to date the material included. In addition, a new section on low level radioactivity in materials as related to the problems of radiological measurements has been added. This topic is important because of the problems arising from the contamination, or possible contamination, in the last decade of a great many of the materials used in the construction of counting equipment, shields, and in the reagent chemicals employed in radioactivity measurements.

Clinical Dosimetry (Report 10d)—Much of the Commission's work on clinical dosimetry is brought together in this report. Included is an extensive discussion of practical calibration procedures and the determination of dose along the central ray. Depth dose data relative to stationary and moving-field therapy have been critically analyzed, as have the conversion data necessary to relate ionization measurements to absorbed dose.

The principal effort has been toward the definition of nomenclature and the indication of methods. While some examples are given and data are provided for these, in general the reader is referred to other published data. The report considers ways of increasing the accuracy and comparability of results in clinical dosimetry. The discussion includes not only the physical aspects of dose measurement but also the wider subject of planning treatment in such a way as to deliver the prescribed absorbed dose to a defined "target volume." It also includes comments upon the common sources

of error in clinical dosimetry and discusses the information which should be recorded during treatment and that which should be reported about any new treatment technique. Appendices to this report include pertinent material taken from other reports in this series.

Radiobiological Dosimetry (Report 10e)—This report deals primarily with radiobiological dosimetry, and considers methods of improving the accuracy and intercomparability of absorbed dose measurements in radiobiology. It is in effect a handbook for the experimental radiobiologist. It emphasizes the great importance of planning the experimental work in a way which makes the dosimetry easier and more accurate and it illustrates how this can be done.

Methods of Evaluating Radiological Equipment and Materials (Report 10f)—This is the first of a new group of ICRU reports dealing with methods of evaluating radiological equipment and materials. It includes a revised discussion on the measurement of focal spots and new sections on grids, image intensifiers and body section equipment.

Operating Funds

Throughout most of its existence, the ICRU has operated essentially on a voluntary basis, with the travel and operating costs being borne by the parent organizations of the participants. Recognizing the impracticality of continuing this mode of operation on an indefinite basis, operating funds were sought from various sources in addition to those supplied by the International Society of Radiology.

Prior to 1959, the principal financial assistance to the ICRU had been provided by the Rockefeller Foundation which supplied some $11,000 to make possible various meetings. In 1959, the International Society of Radiology increased its contribution to the Commission to $3,000 to cover the period until the Tenth Congress. In 1960, the Rockefeller Foundation supplied an additional sum of some $4,000 making possible a meeting of the Quantity and Units Committee in 1960.

In 1960 and 1961 the World Health Organization contributed the sum of $3,000 each year to the Commission for carrying forward its work. This was increased to $4,000 in 1962. It is expected that this sum will be allocated annually, at least for the next several years. In addition, the WHO has provided substantial assistance to the Commission in providing meeting space, secretarial services, etc., for the meetings held in Geneva and Montreux.

In connection with the Commission's Joint Study with the ICRP, the United Nations allocated the sum of $10,000 for the joint use of the two Commissions for the purpose of carrying out their second study. This fund has been administered by the ICRP.

The most substantial contribution to the work of the ICRU has come from the Ford Foundation through the particular efforts of Dr. Paul Pearson. Effective in December 1960, the Ford Foundation made available to the Commission, the sum of $37,000 per year for a period of five years. This money is to be used for such items as travel expenses to meetings, for secretarial services and other operating expenses. To a large extent, it is because of this grant that the Commission has been able to hold the several meetings considered to be necessary to move forward actively with its program.

The International Atomic Energy Agency has allocated the sum of $6,000 per year for use by the ICRU. It is expected that this sum will be allocated annually, at least for the next several years.

A valuable indirect contribution has been made by the U.S. National Bureau of Standards where the Secretariat has resided. The Bureau has provided substantial secretarial services, reproduction services, and travel costs in the amount of several thousands of dollars.

The Commission wishes to express its deep appreciation to all of these and other

organizations that have contributed so importantly to its work.

MEMBERSHIP

Changes in ICRU membership are as follows:

Resigned: Dr. L. H. Gray, member since 1953 and Vice-Chairman since 1956 (Elected Senior Advisor).

Withdrawn because of ill health: Dr. K. K. Aglintsev, member since 1959.

Deceased: Dr. G. Failla, member since 1950, Senior Advisor, 1959–62.

Elected Member Emeritus: Dr. Rolf Sievert.

Elected Senior Advisor: 1962–1965. Dr. B. Rajewsky; Dr. W. Oosterkamp; Dr. L. H. Gray.

New Members, 1962–1965: V. A. Petrov, USSR; K. Liden, Sweden; J. Boag, United Kingdom.

Continuing Members, 1962-1965: A. Allisy, France; R. H. Chamberlain, USA; F. Ellis, United Kingdom; H. Franz, Germany; H. E. Johns, Canada; H. H. Rossi, L. S. Taylor, USA; M. Tubiana, France; H. O. Wyckoff, USA; H. Holthusen, Germany (Member Emeritus)

Commission Officers, 1962–1965: L. S. Taylor, Chairman; M. Tubiana, Vice-Chairman; H. O. Wyckoff, Secretary; W. Ney, Technical Secretary (not a member of the Commission).

NEWS ITEMS

AMERICAN ROENTGEN RAY SOCIETY ELECTS OFFICERS

At the Sixty-third Annual Meeting of the American Roentgen Ray Society held at the Shoreham Hotel, Washington, D. C., October 2 to October 5, 1962 the following officers were elected: President, Dr. Earl E. Barth, Chicago, Illinois; President-Elect, Dr. Ralph M. Caulk, Washington, D. C.; First Vice-President, Dr. Arthur C. Singleton, Toronto, Ontario, Canada; Second Vice-President, Dr. George Cooper, Charlottesville, Virginia; Secretary, Dr. C. Allen Good, Rochester, Minnesota; Treasurer, Dr. Stephen W. Brown, Augusta, Georgia. The new Chairman of the Executive Council is Dr. J. P. Medelman, 110 Birchwood Avenue, Birchwood, White Bear Lake 10, Minnesota.

The Sixty-fourth Annual Meeting of the Society will be held at the Queen Elizabeth Hotel, Montreal, Quebec, Canada, October 8 to October 11, 1963.

SOCIETY FOR PEDIATRIC RADIOLOGY

At the recent meeting of the Society for Pediatric Radiology held on October 1, 1962 in conjunction with the Sixty-third Annual Meeting of the American Roentgen Ray Society at the Shoreham Hotel, Washington, D. C., the following officers were elected: President, Dr. John W. Hope, Philadelphia, Pennsylvania; President-Elect, Dr. R. Parker Allen, Denver, Colorado; Secretary-Treasurer, Dr. John L. Gwinn, Children's Hospital, Los Angeles 27, California.

The next meeting will be held at the Queen Elizabeth Hotel, Montreal, Quebec, Canada, October 7, 1963.

INTERNATIONAL CLUB OF RADIOTHERAPISTS

At its last meeting held in Montreal during the Tenth International Congress of Radiology, Dr. J. A. del Regato was elected President of the International Club of Radiotherapists succeeding Dr. Jean Bouchard of Canada. Dr. Pierluigi Cova, from Milan, was elected Secretary for the European section and Dr. Jose Noriega-Limon, from Mexico, Secretary for the Americas.

CANADIAN NUCLEAR ASSOCIATION

The Canadian Nuclear Association is sponsoring an International Conference on the Operating Experiences and Future Development of Power Reactors and on Radioisotopes at the Queen Elizabeth Hotel, Montreal, Quebec, Canada, May 27, 28 and 29, 1963.

Dual technical and management sessions will be held, with papers presented by well known and highly qualified persons from abroad and from Canada. Panel discussions on subjects of interest to both management and technical personnel will be included in the program.

All inquiries should be forwarded to the General Manager, Canadian Nuclear Association, 19 Richmond Street West, Toronto 1, Ontario, Canada.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

Head

Leeds, N., and Seaman, W. B. Fibrous dysplasia of the skull and its differential diagnosis; a clinical and roentgenographic study of 46 cases. *Radiology*, Apr., 1962, *78*, 570–582. (Address: Wm. B. Seaman, M.D., Columbia-Presbyterian Medical Center, 622 West 168th Street, New York 32, N. Y.)

The skull is a frequent site of involvement by fibrous dysplasia and the skull changes are often the only manifestation of the disease. The condition is easily recognized in many instances but it can simulate, and be imitated by numerous other conditions, particularly the hyperostoses associated with a meningioma. To further increase our knowledge of the natural history and roentgenographic appearance of this disease, the authors present a detailed study of the roentgenographic findings and clinical records of 46 patients with fibrous dysplasia involving the skull and facial bones. The study comprises 24 males and 22 females, from 2 to 68 years of age. Material for microscopic confirmation was available in 16 cases, while in the remainder fibrous dysplasia was considered the correct diagnosis based on characteristic roentgenographic and clinical findings and lack of progression of the lesions.

The most common presenting symptom was asymmetry of the skull or facial bones (21 patients), followed next by an ophthalmologic group of symptoms (7 patients) including decreasing vision, proptosis, scotoma, and epiphora. In 11 patients the findings of fibrous dysplasia were incidental. Although others have reported symptomatic narrowing of neuro-foramina at the base of the skull and proliferation of temporal bone producing loss of hearing by either compression of the nerve or obstruction of the external auditory canal, such was not encountered in this study. A pathologic fracture led to the discovery of the disease in 4 patients, 3 of whom displayed the complete syndrome of Albright.

A singularly important aspect of this study is that it was possible to roentgenographically follow the natural history of the disease in 15 patients, for a period of 6 to 39 years, with 1 patient coming to autopsy. Roentgenographic progression was slight to equivocal in all but 2 cases. In 1 of these cases additional growth continued between ages 9 and 13 years and in the other case between ages 12 and 25 years. Their observations support the opinion of others that progression of fibrous dysplasia, when it occurs, takes place during the years of growth.

The roentgenographic appearance of the skull involved by fibrous dysplasia is variable, and depends on the presence or extent of metaplastic bone in the fibrous tissue. The involved areas therefore may be radiolucent (11 cases), sclerotic (17 cases), or present a mixed type of involvement (18 cases). The radiolucent or cystic type is usually found in the calvaria and may extend across the cranial sutures. A peripheral zone of sclerosis, of varying width, may be present which can simulate an epidermoid inclusion cyst. The important feature of the radiolucent type is that there is diploic widening and bulging of the outer table, with little or no involvement of the inner table, which serves to differentiate it from meningioma. This feature frequently will not be appreciated unless a tangential view is obtained. The sclerotic type is usually diffuse and commonly involves the base of the skull and the wings of the sphenoid. The mixed type may involve a considerable area of the skull, but involvement of the entire skull occurred in only one patient.

The majority of authors agree that fibrous dysplasia is most likely to be confused with a meningioma, particularly a plaque-like meningioma of the sphenoid bone and the intraosseous meningioma arising from a microscopic dural focus. In some cases roentgenologic differentiation is impossible. However, in general, the distinction between these two conditions can be made with ease. Age is a valuable aid since fibrous dysplasia is a disease of childhood, while meningiomas as a rule occur during adult life. Differentiation is further simplified when the vault is the site of the lesion. A meningioma in this location presents a circumscribed bony reaction, beginning in the inner table, and frequently results in an enostosis. The lesion of fibrous dysplasia is usually predominantly cystic, beginning in the diploe, and expands the outer table almost never encroaching on the intracranial contents. In the case of a sclerotic lesion involving a wing of the sphenoid, the localization of the sclerosis in only a portion of the wing and an abrupt transition to normal bone are more characteristic of a meningioma.

The authors conclude with a discussion of the essential feature of a number of additional hyperostosing lesions of children and adults, with emphasis on differentiation from fibrous dysplasia. The original article is recommended to the interested reader.—*Edward B. Best, M.D.*

Scatliff, J. H., and German, W. J. Pantopaque ventriculography with cinefluorography; a technical note. *Radiology*, Mar., 1962, *78*, 465–467. (Address: 789 Howard Avenue, New Haven 4, Conn.)

Opacification of the midline cerebral ventricles with pantopaque has been recommended when air ventriculography has been unsuccessful. One or two cc. of pantopaque is placed in a lateral ventricle through a ventricular catheter and advanced to the frontal horn under fluoroscopic control. With slow extension of the head, the pantopaque passes through the foramen of Monro and then opacifies successively the third ventricle, the aqueduct of Sylvius and the fourth ventricle.

The authors have found cinefluorography to be helpful in improving diagnostic accuracy, since the pantopaque often moves too rapidly through the aqueduct and fourth ventricle for adequate spot roentgenography. With the patient either sitting or prone, exposures in both anteroposterior and lateral projections are made, using either 35 mm. or 16 mm. cine film. On the 5 inch image-amplified field, the sella turcica, clivus, and petrous pyramids serve as landmarks to indicate deviation of the contrast-filled aqueduct and ventricles from their normal position.—*R. F. Bowman, Jr., M.D.*

Loeb, Carlo, and Favale, Emilio. Contralateral EEG abnormalities in intracranial arteriovenous aneurysms; a pathophysiological interpretation. *A.M.A. Arch. Neurol.*, Aug., 1962, *7*, 121–128. (From: Department of Neurology and Psychiatry, Laboratory of EEG, University of Genoa, Genoa, Italy.)

Electroencephalography (EEG) and angiography were performed in 23 cases of supratentorial arteriovenous aneurysms. Four cases are presented in which clinical and/or EEG data suggested contralateral localization subsequently disproved by angiographic and surgical controls.

A review of the literature revealed a 3.5 per cent incidence in which EEG abnormalities were confined to, or were most prominent over, the unaffected cerebral hemisphere.

To explain the functional alteration in the hemisphere contralateral to the aneurysm, wherefrom both clinical and EEG abnormalities could issue, it is postulated that an ischemic hypoxia is created by the shunt action—"sucking action" of the arteriovenous aneurysm.—*William C. McCarty, Jr., M.D.*

Leslie, Eugene V., Smith, Bernard H., and Zoll, John G. Value of angiography in head trauma. *Radiology*, June, 1962, *78*, 930–939. (Address: Dr. Eugene V. Leslie, 462 Grider Street, Buffalo 15, N. Y.)

Cerebral angiography is a reasonably safe procedure which affords a precise diagnosis in a multiplicity of post-traumatic entities. In general, one can distinguish angiographically the extradural from the subdural hematoma. These extracerebral hematomata can further be differentiated from the intracerebral mass lesions, namely the more severe cerebral contusions and the intracerebral hematomata.

Most instances of extradural hematoma are associated with linear fracture of the parietal or temporal bone with resultant severance of the middle meningeal artery or one of its branches. Occasionally when the bleeding is largely venous the clinical picture will not lead to immediate surgical intervention. In this instance angiography will reveal the true situation. It is important that a common carotid puncture should be done to permit visualization of the middle meningeal artery. Classically there is seen displacement of the anterior cerebral artery to the opposite side, medial displacement of the middle cerebral artery, and a lentiform avascular area lying extracerebrally over the convexity of the brain. Displacement of a dural sinus inward from the vault has the same localizing and diagnostic significance. If an internal carotid artery injection is done, the middle meningeal artery will not be visualized but a lentiform avascular area over the hemisphere, seen within a short interval following trauma, would suggest that this is an extradural hematoma.

When injury results in subdural but extracerebral hematoma, angiography will show: (a) an avascular extracerebral area which will distinguish these lesions from intracerebral lesions; (b) the typical lentiform shape of the extradural hematoma, and, on occasion, displacement and possible extravasation of contrast material from the middle meningeal artery or a dural sinus; (c) a convex upward appearance of the brain in acute subdural hematoma; (d) elevation of the middle cerebral artery in basilar subdural hematoma; and (e) straightening of the medial margin of the hematoma in a subacute subdural hematoma, which proceeds to the convex inward contour of the medial surface and thus a lentiform avascular area in the chronic stage. The anteroposterior view is usually more informative than the lateral view, and in some instances an oblique view may be the only view to reveal the findings.

Cerebral contusion with or without laceration may occur independently or in association with extracerebral hematoma with the occipital, frontal, and temporal poles being most frequently affected. The angiogram will show an avascularity of the brain in the involved area due to edema which, if sufficiently localized, will act as a space-occupying mass and shift the adjacent opacified vessels. An intracerebral hematoma will also show as an avascular mass lesion and at times surgical exploration may be required to distinguish this from the localized contusion with or without laceration.

Post-traumatic internal carotid thrombosis, although rare, is important to recognize as this is a remedial lesion requiring prompt surgical attention. It may occur here in persons with head injury and no recognizable trauma to the neck and is due to intimal injury in the carotid artery which permits a mural thrombus to originate and subsequently propagate. The angiogram will show the occlusion of the artery. Dural sinus thrombosis may rarely occur after head trauma but a more common cause is mastoiditis.

Traumatic caroticocavernous fistulae result from injury to the wall of the internal carotid artery within the confines of the cavernous sinus and may be caused by basal skull fracture or a penetrating wound. Contrast medium will show the arteriovenous communication but little of the medium will pass distal to the shunt.

The authors conclude that cerebral angiography is a safe, simple, and precise diagnostic method. When tempered with clinical judgment, its extended use in craniocerebral trauma is urged.—*Donald N. Dysart, M.D.*

Tatelman, Maurice, and Sheehan, Sheila. Total vertebral-basilar arteriography via transbrachial catheterization. *Radiology*, June, 1962, *78*, 919–929. (From: Wayne State University College of Medicine, 1401 Rivard Street, Detroit 7, Mich.)

There has been an increasing awareness of the need for complete angiographic study of all four major arteries supplying the brain in the evaluation of cerebral vascular disease. Since direct percutaneous puncture of the vertebral arteries is inadequate for total visualization, the authors have developed a bilateral transbrachial approach using percutaneous catheter insertion. This allows evaluation of atherosclerosis as well as the effect of cervical spondylosis on the vertebral arteries. The described technique was found superior to other previous direct and indirect techniques. An important feature is visualization of each vertebral artery with injection in the neutral position as well as with the head turned to each side. The latter positions are particularly important in demonstrating the pressure effect of cervical spondylosis. In addition to bilateral study of the vertebral arteries, the carotid arteries were also studied by direct percutaneous puncture either on the day preceding or the day after the vertebral study.

The series includes 220 consecutive cases of which 70 per cent were examined for suspected vascular occlusion or insufficiency. Approximately 10 per cent were studied to evaluate cervical spondylosis, and approximately 10 per cent to investigate intracranial hemorrhage. Complications were rare and were transient in 4 out of 5 patients.

The results of the study indicate that this method of vertebral-basilar artery study finds its greatest usefulness in the evaluation of: vascular insufficiency, usually caused by medial arteriosclerosis; intimal atherosclerosis with or without thrombosis; and extrinsic compression of the vessels, chiefly by cervical osteophytes. Medial arteriosclerotic changes were noted in approximately one-third of the cases. This condition produces dilatation, elongation, and tortuosity of the arteries and causes insufficiency because of loss of adequate pressure in the dilated vessels. At times, sharp kinking may further compromise the blood flow to the brain. Atherosclerosis with intimal changes, producing irregularity of narrowing of the vessels, was encountered less often. The most frequent change was a single narrowed segment near the origin of the vessels; but at times, significant narrowing was noted at several levels, usually near the origin. Complete vertebral artery occlusion occurred in 8 cases. Seven were at the origin of the vessel with 2 on the right side and 5 on the left. The authors have no explanation for the higher incidence on the left.

External compression of the vertebral artery by cervical osteophytes was encountered in nearly 20 per cent of the series. In all cases with compression, the clinical symptoms were definitely felt to be related to the compression effect. It is interesting to note that, in the cases illustrated, evaluation of the degree of compression by cervical osteophytes is achieved only on the recommended rotated views.—*Edward B. Best, M.D.*

Neck and Chest

Saliba, Alex, Beatty, Oren A., and Pacini, Luigi. Pulmonary histoplasmosis associated with pulmonary tuberculosis. *South. M. J.*, Mar., 1962, *55*, 249–256. (From: The District Two State Tuberculosis Hospital, Louisville, Ky.)

The authors reviewed the literature and found that it is not uncommon for histoplasmosis to accompany pulmonary tuberculosis. Extensive skin testing programs and serologic studies in sanatoria have been used. Some cases of cavitary histoplasmosis have negative skin tests, and concomitant tuberculosis was found to be 20 per cent in one study. In another study of 80 patients with positive serologic tests for histoplasmosis 52 per cent had active tuberculosis. It is now generally recognized that cavitary histoplasmosis is not unusual in tuberculosis hospitals. Having diagnosed tuberculosis by cultural methods the physician may be completely unaware of concomitant fungus infection; however, the reverse is usually not true.

The study was divided into 3 groups. The first group included cases with active tuberculosis and active histoplasmosis. The diagnosis of both is important from a therapeutic standpoint and they are very similar both clinically and roentgenologically. The histoplasmosis may progress while the tuberculosis is being treated and the mortality of this form of histoplasmosis is high unless it is treated. The treatment for histoplasmosis used by this group is with amphotericin B as follows: a dose of 1 mg./kg. is given 3 times weekly for 16 weeks starting with one-fourth of this dose. Serologic tests for histoplasmosis have been as high as 6 per cent in tuberculosis sanatoria with one-third of these later proven by cultural methods or histology to be histoplasmosis. The higher the serologic titer the more likely is the presence of active histoplasmosis. Before surgery for residual cavitary disease, both the tuberculosis and the histoplasmosis should receive adequate medical management.

The second group included the most common association of active tuberculosis and inactive histoplasmosis. The histoplasmosis in this group was

revealed by positive skin tests and/or serology. Positive serology may suggest residual activity. Roentgenologically, histoplasmosis may be suggested by large "mullberry" or "stippled" paratracheal calcifications, scattered parenchymal calcifications and splenic calcifications. Tuberculosis is not the most common cause of pulmonary calcifications. Active sputum studies may prove some of these cases to be active histoplasmosis.

The third group included cases of suspected pneumomycoses in which the presence of tuberculosis had been ruled out as far as possible and the causative organism had not been found. Blastomycosis and coccidiomycosis, as well as histoplasmosis, are considered; however, histoplasmosis most closely resembles tuberculosis. A therapeutic trial of amphotericin B may aid in diagnosis. Skin tests and complement fixation tests are only screening tests and diagnosis rests on isolation of *Histoplasma capsulatum.*

The authors conclude that the diagnosis of concomitant histoplasmosis and tuberculosis is of more than academic interest.—*Gerald M. Wohlfeld, M.D.*

BAHK, Y. W. Pulmonary paragonimiasis as a cause of Loeffler's syndrome. *Radiology*, Apr., 1962, *78*, 598–601. (From: Department of Radiology, Chonnam University Medical School, Kwangju, Chonnam, Korea.)

The occurrence of Loeffler's syndrome in 3 cases of pulmonary paragonimiasis is reported. The ova of *Paragonimus westermanii* were demonstrated in the sputum of 2 patients but were not found in the sputum or stools of the third patient. Charcot-Leyden crystals in the sputum and positive skin tests aided in establishing the diagnosis. There was persistent eosinophilia of 25 to 39 per cent in the peripheral blood in all 3 cases. Chest roentgenograms revealed fleeting, patchy lung densities, some pleural effusion, and in 2 patients the typical cystic lung lesions.

A hyperergic reaction due to the presence of *Paragonimus westermanii* is the actual pathogenetic mechanism, as is the case with other allergens and organisms. This is borne out by the fact that the cystoidal lesions typical of paragonimiasis developed at the sites of the Loeffler's pneumonia synchronously with the appearance of ova in the sputum in 1 of the cases.—*A. W. Sommer, M.D.*

DRAGONI, G., and SALVINI, E. I tumori connettivali maligni primitivi del polmone. (Primary malignant mesenchymal tumors of the lungs.) *Radiol. med.*, Feb., 1962, *48*, 138–150. (Address: Dott. Prof. Giovanni Dragoni, Via Venezian, 14, Milano, Italy.)

Among the primary neoplastic malignant lesions of the lungs, those of mesenchymal origin are extremely rare.

Sarcomas of the lung are found mainly in young individuals of the male sex. They may originate from the connective tissue of the alveoli, of the interstitium, of the submucosa of the bronchi, from the adventitia of the vessels and from the subpleural tissue. Development is eccentric and quite expansive with invasion of the surrounding parenchyma. In its progression, the sarcoma involves and destroys the various structures of the lung parenchyma, bronchi and vessels, frequently causing hemorrhages, necrosis and bronchoarterial fistulae.

Histologically the sarcomas are divided into fusiform cell, round cell, polymorph cell and giant cell types. Cases of myxomatous sarcomas, angioblastic sarcomas, fibrosarcomas, and chondro-mixo-fibrosarcomas are also observed.

In a series of nearly 700 epithelial neoplasms of the lungs studied in the Department of Radiology of the Medical School of the University of Milan, there were only 5 cases of sarcoma, which are reported in detail by the authors.

The clinical findings are not characteristic and are different in each patient. The roentgen findings are also not always contributory. The most frequent finding is a lobar dense, homogeneous opacity of the left lower lung or the right upper lobe with smooth convex contours facing the normal parenchyma and with secondary displacement of the mediastinal shadows toward the opposite side. The lesion grows and expands very rapidly.—*A. F. Govoni, M.D.*

O'BRIEN, PAUL S., ROBICSEK, FRANCIS, GLENN, JOHN C., JR., TAYLOR, FREDERICK H., and SANGER, PAUL W. Anomalous venous drainage of the right lung into the inferior vena cava: report of three cases. *South. M. J.*, Mar., 1962, *55*, 262–264. (Address: 2000 East Fifth Street, Charlotte, N. C.)

This article emphasizes the value of the plain posteroanterior chest roentgenogram in diagnosing this condition. In all 3 cases presented there was a crescent-shaped vascular density adjacent to the right heart border which deviated from the lateral superior position to a more medial location. This vascular shadow increased in diameter as it descended toward the cardiodiaphragmatic angle.

In the 3 cases, the diagnosis was made from the plain roentgenograms and confirmed by catheterization studies. All cases were adults; clinical cardiac signs were minimal; and none had evidence of right ventricular pressure elevation or heart failure. In 2 cases the anomalous drainage was associated with dextroversion and dextroposition of the heart plus anomalies of the right lung.—*R. Lynn Turner, M.D.*

MEDD, W. E., and KINMONTH, J. B. Congenital tricuspid stenosis: a case treated by open operation. *Brit. M. J.*, Mar., 1962, *1*, 598–

600. (From: The Cardiac Department and the Surgical Professional Unit, St. Thomas's Hospital, London, England.)

The clinical, laboratory and operative findings are described in a patient with tricuspid stenosis and an atrial septal defect, who improved considerably following dilatation of the tricuspid orifice and closure of the atrial septal defect.

The patient is a 9 year old girl with a lifetime history of cyanosis and dyspnea and 2 episodes of syncope. Physical examination revealed cyanosis and clubbing of both the upper and lower extremities. Pulse and blood pressures were normal. The apical pulse was slightly outside the midclavicular line and there was a systolic thrill and murmur to the left of the lower sternum.

Chest roentgenogram showed decreased pulmonary vasculature. The electrocardiogram was regarded as within normal limits, but the axis suggested left ventricular preponderance, and the P waves right atrial hypertrophy. Cardiac catheterization was performed on 2 occasions. The first, 3 years earlier, revealed a left to right shunt at the ventricular level and an average gradient of 2.75 mm. of Hg across the tricuspid valve. The second procedure revealed a ventricular septal defect without a left to right shunt and a gradient of 0–5 mm. of Hg across the trisucpid valve. Angiocardiography demonstrated a right to left shunt via a high atrial septal defect.

At surgery the right atrium was noted to be large, the right ventricle small. An abnormal coronary artery ran across the infundibulum and rendered ventriculotomy inadvisable. On inserting a finger into the right atrium, a 1.5 cm. high atrial septal defect and tricuspid stenosis, which would admit only the distal interphalangeal joint, were noted. A jet of blood, felt by the tip of the finger, suggested a ventricular septal defect. Under cardiopulmonary by-pass the atrial septal defect was closed with continuous sutures reinforced with interrupted sutures and the tricuspid orifice was dilated until it would admit the proximal interphalangeal joint.

The postoperative course was uneventful. There was initially a slight rise in veinous pressure which may have been due to the small capacity of the right ventricle. Cyanosis and diminished exercise tolerance disappeared within 6 months. The systolic murmur remained and in addition a to-and-fro murmur was noted in the pulmonic region.

The differential diagnosis in a cyanotic patient with right atrial hypertrophy without electrocardiographic evidence of right ventricular hypertrophy includes tricuspid atresia, Ebstein's malformation, pulmonary atresia with intact ventricular septum and small right ventricle, congenital tricuspid stenosis and isolated hypoplasia of the right ventricle and tricuspid valve. Tricuspid atresia and pulmonary atresia were excluded by passage of the catheter into the right ventricle and pulmonary artery. Ebstein's malformation is unlikely due to the absence of the usual roentgenologic and electrocardiographic findings. The differentiation of tricuspid stenosis and isolated hypoplasia of the right ventricle and tricuspid valve would rest on the finding of a diastolic gradient across the valve which in this case varied between 0 and 5 mm. of Hg.

Though this patient improved considerably following the combined procedure of closure of the atrial septal defect and dilatation of the tricuspid orifice, the possibility that the right ventricle may not be able to accommodate the increased flow must be considered in future cases and it may not always be advisable to close the defect completely.—*John P. Tampas, M.D.*

Garamella, Joseph J., Schmidt, W. Robert, Jensen, Nathan K., and Lynch, Michael F. (Minneapolis, Minnesota.) Traumatic aneurysms of the thoracic aorta: report of four cases, including one of spontaneous rupture into the esophagus. *New England J. Med.*, June, 1962, *266*, 1341–1348.

Four cases of traumatic aneurysms of the thoracic aorta are reported. They were treated surgically, three successfully. All of the aneurysms were the result of nonpenetrating trauma, three of which resulted from automobile accidents. These four post-traumatic cases represent 25 per cent of the total experience of the authors with thoracic aneurysms.

The characteristic location of post-traumatic aneurysms is distal to the subclavian artery in the isthmus between it and the ligamentum arteriosum and first intercostal arteries. All four of these cases occurred at this site.

The fatal case in this series had a history of a chest injury 8 years earlier, with hemorrhage due to rupture of the aneurysm into the esophagus 10 days before admission. On the third and fourth days after admission he again bled profusely and subsequent surgery disclosed the traumatic aneurysm extending from just distal to the left subclavian artery to 5 cm. above the diaphragm. It had eroded the esophagus, and there was an abscess in the clot owing to the fistulous communication with the esophagus. Massive bleeding from the aneurysm into the esophagus began during surgery and handicapped the procedure. The aneurysm was excised and multiple bleeding points on the chest wall were sutured or cauterized. The patient's general immediate postoperative condition was fair. Death occurred on the second postoperative day after massive melena and perforation of the ileum.—*Lois Cowan Colllins, M.D.*

Nordenström, Björn, Ovenfors, Carl-Olof, and Törnell, Gunnar. Coronary angiography in 100 cases of ischemic heart disease. *Radiology*, May, 1962, *78*, 714–724. (From: Karolinska Sjukhuset, Stockholm 60, Sweden.)

The authors present the results and conclusions of their experience with 100 patients in whom coronary angiography was performed. An important feature of their technique is that injection and filling are accomplished during an increase in intrabronchial pressure to 40 cm. of water. This effectively reduces blood flow in the aorta and allows layering of the contrast medium. The method involves percutaneous catheter insertion with positioning of the tip above the aortic valves. The patient is placed before a film changer, in the left antero-oblique position. With elevations of the intrabronchial pressure, either by Valsalva maneuver or by inflation of the lungs, 1 ml./kg. of body weight of a 76 per cent solution of urografin is injected within 3 seconds.

The first 100 patients examined by this method include patients under 60 years of age with previous myocardial infarction; all patients under 60 with angina; patients with angina and valvular aortic stenosis; subjects of certain professions, as for instance pilots, with severe electrocardiographic changes; clinically operable patients; and patients for assessment after medical treatment or operation. The authors require normal kidney, liver and pulmonary function tests and normal blood values before angiocardiography. The contraindications include the presence of acute infection, systemic diseases, decompensation of the heart, and all signs of serious types of arrhythmia.

A total of 25 cases of abnormal coronary vessels were identified; 12 on the left, and 13 on the right. The sites of narrowing on the left include the main coronary artery as well as the anterior descending and circumflex branches. However, the division between the anterior descending and the circumflex branch seems to be a classical site of localized atheromatosis on the left. The most common location for atheromatous changes in the right coronary artery is a segment several centimeters long, beginning 2 or 3 centimeters distal to its origin from the aorta. The reason for this particular localization is unknown but the authors feel that this is related to the position of the artery in the atrioventricular groove where alternating opposite movements of the right atrium and ventricle produce a localized strain on the vessel.

Collateral vessels around an area of total or partial occlusion were of two types: those with a winding course and a smooth wall; and those with an irregular course, narrow lumen, and uneven walls. The latter type of vessel is presumed to be an older collateral. The direction of flow in different areas is important and easily determined by careful study of the angiograms. The presence and site of occlusion can be demonstrated by reversal of normal blood flow into the area distal to an occlusion.

Diffuse atheromatosis without occlusion was noted to be the main type of change in ischemic heart disease. The capillary phase is of special interest in these cases and it is the authors' opinion that the myocardiogram effect obtained in ischemic heart disease is more marked than in other cases. In several patients this effect was noted to correspond with the site of clinically suspected myocardial infarction. To date, the visualization of the coronary veins has not been of diagnostic value.

In conclusion, the authors emphasize that the accurate preoperative demonstration of the amount and extent of atherosclerotic changes in the coronary arteries is a prerequisite to successful vascular surgery.—*Edward B. Best, M.D.*

Sulavik, Stephen. Mediastinal crunch (Hamman's sign). *GP*, July, 1962, *26*, 104–105. (From: Bronx Veterans Administration Hospital, New York, N. Y.)

Hamman's description of fine auscultatory crepitations synchronous with the heart beat was felt to be characteristic if not diagnostic of mediastinal emphysema.

The author describes similar signs occurring in left-sided pneumothorax, dilated lower esophagus, bullous emphysema of the lingular segments, pneumoperitoneum with a high left diaphragm and gastric dilatation. Characteristically, the crunching, bubbling, tapping sounds are likened to the "crackling of dry cellophane" and are heard best along the left sternal costal border over the heart. The probable mechanism of this mediastinal crunch is the beating of the heart against a myriad of minute air bubbles located between the anterior cardiac surface and the chest wall.

The author concludes that, if Hamman's sign is accompanied by subcutaneous emphysema of the neck and chest, the diagnosis of mediastinal emphysema can be reasonably assured.—*Ned B. Hornback, M.D.*

Lagarde, C., Guetton, J., and Laurens, G. Les adénopathies médiastinales régressives de l'adulte jeune: étude d'une série personnelle de 39 observations. (Regressive mediastinal adenopathies of the young adult: study of a personal series of 39 cases.) *J. de radiol., d'électrol. et de méd. nucléaire*, Mar.–Apr., 1962, *43*, 137–147. (From: Service de Radiologie de l'Hôpital Maritime Sainte-Anne, Toulon, France.)

A new entity has recently been isolated from the extensive field of mediastinal adenopathies; it encompasses those cases which are usually found by routine roentgenologic check-ups, are commonest in young adults, and regress spontaneously in 1 to 24 months. The incidence of the disease is placed at 0.12 per thousand.

The authors analyze 39 cases reporting that usually the tuberculin reactions are negative or weakly positive, that as a rule there are no pathologic antecedents, nor are there other cases in the families or close associates. Twenty-two of the patients had recently had normal roentgenograms.

Roentgenologically the lymph nodes were of moderate or great size, usually symmetric, and often associated with an enlarged right latero-tracheal lymph node. Frequently reticular or nodular patterns appeared in the lungs. Six of the cases were proved by biopsy of peripheral lesions to be sarcoidosis, leaving the etiology of the remainder in doubt.—*Frank A. Riebel, M.D.*

Bunker, Paul G. The role of dentistry in problems of foreign bodies in the air and food passages. *J. Am. Dent. A.*, June, 1962, *64*, 782–787. (Address: Newberry Building, Aberdeen, S. D.)

The author calls attention to the fact that a high percentage of instances involving foreign bodies in the esophagus or tracheobronchial tree have dental aspects. Thirty per cent of all foreign bodies in the air and food passages of persons of all ages are bones, and in edentulous individuals this percentage rises to 85 per cent. The dentist should warn his patient of this danger at the time the dentures are fitted. Dentures should be kept in good repair and properly fitted to insure good mastication. Patients must wear and use their dentures and should be instructed to chew their food twice as long as when they had their natural teeth. A loose denture itself is a hazard as it may be swallowed, especially if the patient sustains a blow, fall or excitement. An ill-fitting denture causes faulty chewing which may result in a large bolus of meat lodging in the esophagus. This can also happen in the presence of a painful, abscessed tooth. It is the dentist's responsibility to make certain that the denture fits properly and that the patient uses it.

Foreign bodies in the esophagus or tracheobronchial tree are common accidents, and infants are particularly prone to this type of accident. Infants are unable to talk, so a foreign body in the air or food passage may go unrecognized until serious complications develop or death may occur. A persistent wheeze, cough or dyspnea should always suggest the presence of a foreign body in the tracheobronchial tree, whereas dysphagia and excessive salivation should make one suspect a foreign body in the esophagus.—*Douglas S. Kellogg, M.D.*

Abdomen

Oberhauser, E., Matte, H. Orrego, Salinas, A., and Baraona, E. Further studies on intestinal absorption in liver cirrhosis, using an intraintestinal reference substance (polyethylene glycol). *Am. J. Digest. Dis.*, Aug., 1962, *7*, 699–711. (From: The Gastroenterological Unit, Clinical Hospital of the University of Chile, Santiago, Chile.)

Absorption from the intestinal lumen of D-xylose, glucose, fat, and triolein-I^{131} was studied in 9 control subjects and in 9 patients with cirrhosis of the liver. A nonabsorbable reference substance, polyethylene glycol (PEG), was used. The metabolite/PEG index was determined in the test meals and in samples of intestinal contents obtained by jejunal intubation. The results in both groups were compared.

The fatty acids/PEG and triolein-I^{131}/PEG indexes were higher in cirrhotics than in the control group. This was attributed to an altered absorption of fats in patients with liver cirrhosis, already demonstrated by other techniques. The glucose/PEG and D-xylose/PEG indexes in cirrhotics were not significantly different from those in the control group. Normal absorption of glucose and D-xylose, together with evident malabsorption of lipids, leads the authors to suspect that the underlying defect does not involve the intestinal wall. It might be of pancreatic origin or due to deficiency of some other factor, such as insufficient or altered production of bile salts that facilitates digestion and absorption of lipids, while not affecting the absorption of carbohydrates.

In the group of cirrhotics, the volume of intestinal contents was found to be significantly higher than in the control group, which correlates well with the increase in the volume of feces described in these patients and with the increase in the volume of pancreatic secretion after secretion stimulation.

The values for amylase, lipase, and pH in the intestinal contents were similar in the patients with cirrhosis and the control group.

As to the method of using a reference substance, the authors conclude that it is very worthwhile for establishing comparisons of indexes in cases of normal and abnormal absorption, but it probably cannot be applied quantitatively to assess the absorption of a specific metabolite.—*William K. Littman, M.D.*

Monroe, Lee S., and Norton, Richard A. Roentgenographic signs produced by Taenia saginata. *Am. J. Digest. Dis.*, June, 1962, *7*, 519–522. (Address: Scripps Clinic, 476 Prospect Street, La Jolla, Calif.)

The beef tapeworm (Taenia saginata) may be easily demonstrated by roentgen study of the small intestine. The average worm is 12 to 15 feet in length tapering from 1 to 2 mm. in diameter at its neck to approximately 12 mm. in width and from 1 to 2 mm. in thickness at its distal end. The scolex at the anterior end is usually attached in the midportion of the small intestine, and the thicker and demonstrable portion of the worm is predominantly in the ileum. In this respect it varies from the cylindrical roundworms which are usually found predominantly or entirely in the jejunum. The roundworms are shorter (15 to 30 cm. in length) and uniform in caliber as opposed to the tapering Taenia, and the intestinal tract of the Ascaris is often demonstrated by barium. The tapeworm does not have an intestinal tract but may fold upon itself, and a thin line of barium between the two segments of worm may simulate an intestinal tract.

Two cases of roentgenographically demonstrated Taenia saginata are reported and illustrated.—*Lois Cowan Collins, M.D.*

HILLCOAT, B. L. Calcification of the meconium within the bowel of the newborn. *Arch. Dis. Childhood*, Feb., 1962, *37*, 86–89. (From: The Department of Pathology, Brisbane Hospital, Brisbane, Australia.)

The author presents 2 new cases of intraluminal intestinal calcification and briefly reviews the 4 previously reported cases. Biochemical studies were performed on the serum of the infants and mothers as well as biochemical determinations of the meconium. There was a two to three fold increase in the calcium and phosphorus in the meconium of the 2 cases described. One mother and one baby in the 4 reported cases had low levels of serum alkaline phosphatase; the serum calcium and phosphorus levels were normal. Three of the 6 cases had imperforate anus with other congenital abnormalities. One case had a diagnosis of small bowel atresia. One case had stenosis of the small bowel and the remaining case showed functional bowel obstruction. The intraluminal calcifications appeared to be circular concretions of calcium within the meconium. The only evidence of systemic disturbance is the low alkaline phosphatase mentioned above in the 1 infant and 1 mother; however, both had normal serum phosphorus levels.

No theory so far suggested as to the cause of the intraluminal calcification has been proven and none seems to account for all the facts observed.—*James V. Grief, M.D.*

TORIELLO, JULIO. Colangiografía intravenosa de urgencia en el diagnóstico diferencial de la colecistitis aguda. (Prompt intravenous cholangiography in the differential diagnosis of acute cholecystitis.) *Radiología*, Panamá, Mar., 1962, *12*, 61–66. (Address: 11 Calle 2–37 zona 1, Guatemala, C.A.)

Immediate intravenous cholangiography is a practical procedure for the diagnosis of acute cholecystitis. Approximately 30 cases with acute abdominal symptoms, including 10 cases of cholecystitis, were examined by means of intravenous cholangiography. Cholografin 50 per cent was used as the contrast medium. There was no special preparation. Roentgenograms were made in the left anterior oblique projection and were obtained at 5, 30 and 60 minutes, and at 2 and 3 hour intervals after the injection. In some cases, delayed roentgenograms at 4 and 6 hours were also made.

In 40 per cent of the cases, no opacification was obtained. When there was opacification of the gallbladder and the ducts, acute cholecystitis could be ruled out. Visualization of the biliary ducts without visualization of the gallbladder can be taken as evidence of obstruction of the cystic duct. Delayed roentgenograms may be required in these cases in order to avoid erroneous diagnosis. When neither the gallbladder nor the biliary ducts are visualized but cholografin is seen in the colon in the 24 hour roentgenogram, obstruction of the cystic duct and cholecystitis can be suspected.—*Murray M. Friedman, M.D.*

EVANS, J. A., GLENN, F., THORBJARNARSON, B., and MUJAHED, Z. Percutaneous transhepatic cholangiography: discussion of method and report of 25 cases. *Radiology*, Mar., 1962, *78*, 362–370. (From: The New York Hospital-Cornell Medical Center, New York, N. Y.)

Percutaneous transhepatic cholangiography as described is a practical and safe roentgenologic procedure found to be helpful in the differentiation between obstructive and hepatocellular jaundice and for demonstration of the biliary tree in jaundiced patients. It is particularly helpful in the presence of clinical or chemical jaundice, where conventional diagnostic roentgen examination of the gallbladder and bile ducts offers no help.

The main indications for this procedure are: (1) to differentiate between obstructive and nonobstructive jaundice; (2) to diagnose the presence and site of carcinoma of the biliary system; (3) to demonstrate the site and number of calculi in the ducts; (4) to elucidate the status of the biliary tree in cases of congenital biliary atresia; and (5) to investigate certain puzzling cases of the postcholecystectomy syndrome. The two main complications of percutaneous cholangiography are internal bleeding, due to accidental perforation of a blood vessel, and bile peritonitis as a result of seepage of bile into the peritoneal cavity. One instance of each of these complications occurred in the series of 25 cases presented and reviewed by the authors.

In 19 of the patients presented, the examination was successful. All had clinical jaundice and in 13 the liver was enlarged. Three were found to have carcinoma of the ampulla of Vater; 7 had carcinoma of the pancreas; 3 had carcinoma of the common bile duct; and 6 had choledocholithiasis. Of the 6 patients in whom the examination was unsuccessful, all but 1 had clinical jaundice and in 3 the liver was enlarged. There was 1 case of cirrhosis of the liver; 1 of carcinoma of the gallbladder; 1 of carcinoma of the pancreas; 1 of metastasis to the liver; and 2 of choledocholithiasis, each of which had a dilated common duct.

A brief historical review of the world literature is presented, along with 5 case reports from the authors' material which illustrated the value of this procedure. The technique used by the authors is described in detail. It is felt that when the indications are proper and the examination is done in the immediate preoperative period, percutaneous trans-

hepatic cholangiography is of distinct value. It is entirely possible that, with additional clinical experience and with carefully supervised cases, it need not necessarily be followed by immediate surgery provided the patient remains in the hospital under careful observation and competent surgical assistance is readily available if required. The results of the examination along with close collaboration between surgeon and radiologist both in the conduct of the examination and in the immediate post-examination period may well obviate the need for surgery.—*Donald N. Dysart, M.D.*

Gynecology and Obstetrics

Fontaine, R., Warter, P., Weill, F., Dreyfus, J., and Weill, A. La pelvigraphie gazeuse dans les syndromes endocrino-génitaux de l'enfant. (Gaseous pelvigraphy in the endocrine-genital syndromes of children.) *J. de radiol., d'électrol. et de méd. nucléaire*, Mar.–Apr., 1962, *43*, 148–152. (From: Clinique Chirurgicale A, Strasbourg, France.)

When endocrine anomalies appear in the young child, as in macrogenitosomia, genital hemorrhages in the young girl, intersexual states, or in adrenogenital syndrome (even if limited to mere hirsutism), one must search for a secreting tumor or a hyperplastic endocrine gland.

Roentgenology is of use in determining the genotype, bone age, and volume of the pituitary and adrenals. Also hysterosalpingography may be of value.

A less frequently employed but useful technique is gaseous pelvigraphy. The authors find that this is easily performed; after the bladder has been emptied, the abdominal cavity is punctured in the midline just below the umbilicus, and from 200 to 1,000 cc. of CO_2—depending on the patient's age—are introduced. The head of the table is depressed to various angles up to 45° and roentgenograms centering on the coccyx are made. The ovaries and uterus can thus be evaluated.—*Frank A. Riebel, M.D.*

RADIOISOTOPES

Ferguson, Albert B., Jr., Akahoshi, Yoshihiko, Laing, Patrick G., and Hodge, Edwin, S. Trace metal ion concentration in liver, kidney, spleen, and lung of normal rabbits. *J. Bone & Joint Surg.*, Mar., 1962, *44A*, 317–336. (From: The Orthopaedic Department, University of Pittsburgh, and the Mellon Institute, Pittsburgh, Pa.)

In order to provide a baseline for further experimentation the trace ion concentration of cobalt, chromium, nickel, titanium, aluminum and iron present in normal rabbit spleen, liver, kidney and lung was determined by the spectrographic method. The comparison is also made between values reported in the literature for humans and the results found in the rabbit. Detailed charts and tables are presented.

A second set of experiments was then done following implantation of commonly used alloys, and tests made at 6 and 16 weeks on spleen, liver, kidney, lung, adjacent muscle and control muscle. The alloys tested were vitallium, 316 stainless steel, incoloy, A-286 stainless steel, aluminum 2024-T3, titanium zirconium and puron.

In the storage of trace metals the spleen and lung led the list. Between 6 and 16 weeks the spleen showed an increase in storage of ions while the other organs tended to show a gradual decline. Cobalt and nickel were the most active ions. Iron contributed by embedded metal has negligible pickup. No overwhelming effect of any particular alloy or the ion concentration in the vital organs could be discerned. For details the reader is referred to the charts in the original article.—*Martha Mottram, M.D.*

Udvarhelyi, George B. Radiation hypophysectomy with gold-198. *South. M. J.*, Apr., 1962, *55*, 377–384. (From: The Division of Neurological Surgery, The Johns Hopkins University School of Medicine, Baltimore, Md.)

The role of pituitary function and its ablation in cases of carcinoma of the breast with metastasis has been previously discussed. Several methods of accomplishing hypophysectomy are in use: external irradiation with collimated 340 mev. proton beam; implantation with radon seeds, yttrium 90 radioactive chromium phosphate, tridium, palladium and gold 198. The author presents his experience with the transsphenoidal or transethmoidal approach with gold seed implantation. He first implanted the gold seeds into the pituitary of dogs and then studied the effect on the gland.

The transsphenoidal approach was used in the 39 patients included in the study. Under adequate sedation and local anesthesia the implantation trochar was inserted in one nostril and guided through the sphenoidal sinus into the sella turcica. The procedure was done with image intensification fluoroscopy and spot roentgenograms as guides. The needle tip lies between 3 and 6 mm. within the anterior wall of the pituitary fossa depending on sellar size. The seed optimally is 2.5 mm. below the diaphragma sellae in the midline. It should not be closer than 3 mm. from the medial wall of the cavernous sinus. Pre- and postoperative cortisone was given. Unscreened gold seeds were used ranging from 23 to 45 μc in the series.

Thirty of the 39 patients had breast carcinoma. Four were still living when the article was written, one for 11 months, the others for 68, 68, and 47 days. The average survival time for the others was 94

days. Pain relief was marked in 19 cases while in 11 there was only transient improvement.

Four patients with diabetic retinopathy were treated. One had marked improvement, 2 showed no change and 1 died of pneumococcal meningitis 5 days postoperative.

One patient with a chromophobe and one with an eosinophilic adenoma each enjoyed remission of symptoms. Two patients with prostatic carcinoma had no significant change, while a single patient with melanocarcinoma had recurrence of pain in 30 days and finally died.

The author records 2 deaths in this series: 1 from meningitis and 1 from cardiac and respiratory decompensation. No ocular complications occurred. Rhinorrhea was present in 5 patients, 3 of whom had meningitis which was controlled by antibiotics. Seven patients had diabetes insipidus which was controlled with vasopressin (pitressin). In 1 case there was misplacement of the gold seed which finally gravitated into the neck.

The author believes that this procedure compares favorably with any other type of approach, although total destruction of the pituitary gland does not occur.—*George A. Kling, M.D.*

MISCELLANEOUS

TUBIANA, M., LALANNE, C-M., and SURMONT, J. (Villejuif, France.) Total body irradiation for organ transplantation. *Proc. Roy. Soc. Med.*, Dec., 1961, *54*, 1143–1150.

Uniform whole-body exposure to doses of 400–450 rads appears to be well tolerated by man, provided that certain precautions are observed. With such doses, hemorrhages are of a relatively minor nature and easy to control. The risk of the infection is much more serious; it would appear that this danger can be averted by observing strict aseptic precautions and that it is possible for a patient to live a month or more in an atmosphere much more sterile than that of an operating theater.

Under these conditions and by the use of antibiotics, not as a routine measure, but for specific therapy, it appears possible to reduce the risks of infection.—*G. Tievsky, M.D.*

WOODRUFF, M. F. A. (Edinburgh, Scotland.) The outlook for transplantation of the kidney in man. *Proc. Roy. Soc. Med.*, Dec., 1961, *54*, 1150–1153.

It has been said that some 250,000 people die each year as a result of renal insufficiency. It is impossible to estimate how many of these lives could be saved if the problems which at present limit the use of renal transplants were all solved, but the number is certainly considerable. These problems are of four kinds: (1) technical, (2) immunological, (3) storage, and (4) ethical and legal.

The literature concerning these problems is reviewed and a full discussion given.—*G. Tievsky, M.D.*

SMITHERS, D. W. Spontaneous regression of tumours. *Clin. Radiol.*, Apr., 1962, *13*, 132–137. (From: The Royal Marsden Hospital and Institute of Cancer Research, Royal Cancer Hospital, London, England.)

"Spontaneous" tumor regression is a natural phenomenon which has been well authenticated in numerous cases. Regression has been observed most frequently in the following neoplasms: embryonal tumors in children, carcinoma of the female breast, chorionepithelioma, adenocarcinoma of the kidney, malignant melanoma, soft tissue sarcoma, carcinoma of bladder, and carcinoma of ovary. In some cases regression occurs simultaneously in the primary lesion and in the metastases apparently due to general effects on all the tumor tissues present in the patient, seen in the neuroblastomas of children and in chorionepitheliomas, where it may be the result of homograft reaction and hormone dependence. In breast carcinomas spontaneous regression of primary and secondary lesions may occur at the time of the natural menopause, indicating hormone dependence. Smithers believes that such regression in breast carcinoma may be considerably more common than was once thought likely, in view of the fact that few patients in whom the menopause follows closely on a diagnosis of breast carcinoma fail to receive treatment. Hence, if natural regression does occur it is apt to be attributed to the prescribed treatment.

In patients with adenocarcinoma of the kidney where regression occurs it is apparently only in lung metastases in patients who had had their primary tumors removed. In soft tissue sarcomas and carcinomas of the bladder spontaneous regression has been noted in the primary tumor only, and has taken place when no metastases have been present. Smithers suggests that some of the soft tissue sarcomas may be of embryonal character and unstable in nature. Some carcinomas of the bladder may be limited to the presence of an inciting carcinogenic agent—disappearing after such agent is no longer present. In the case of adenocarcinomas of the kidney there may be a very slow rate of growth. Smithers thinks it is possible that kidney tumors, with their peculiar potentiality for shedding groups of well differentiated cells into veins, are peculiarly suited to the production of well differentiated metastases in the lungs. Such metastases are apt to have a low growth potential and may be successfully removed surgically or rarely may undergo regression.—*Samuel G. Henderson, M.D.*

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SURGICAL CORRECTION FOR ANEURYSM of the vein of Galen in 15-month-old patient

Radiographs on Kodak Blue Brand medical x-ray film; surgical procedure photographed on 35mm Kodak Ektachrome film.

Note diagnostic clarity of the radiographs shown here . . . the crisp brilliance of the color transparencies which detail the surgical procedure.

Here are radiography and photography at their best, thanks to precision materials used with precision —Kodak Blue Brand medical x-ray film and 35mm Kodak Ektachrome film—both prime contributors to the advancement of medical research and review.

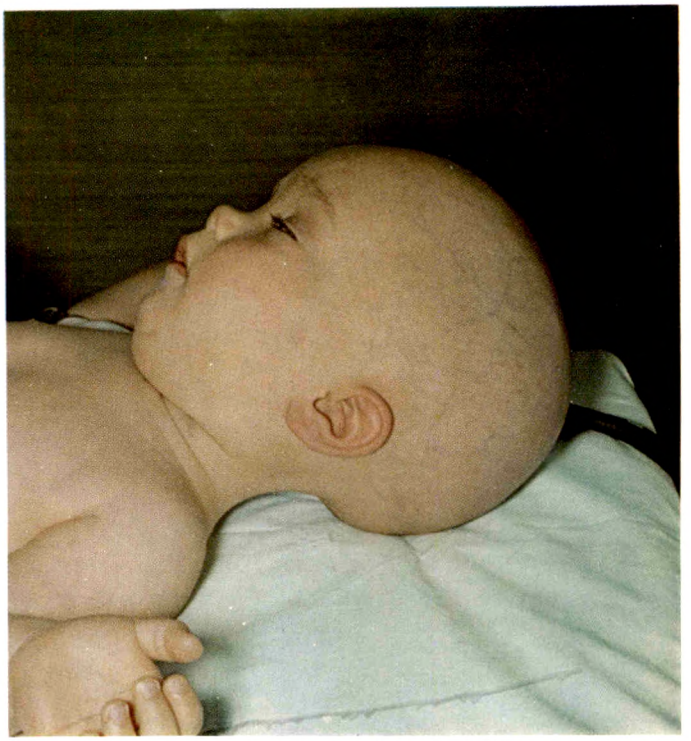
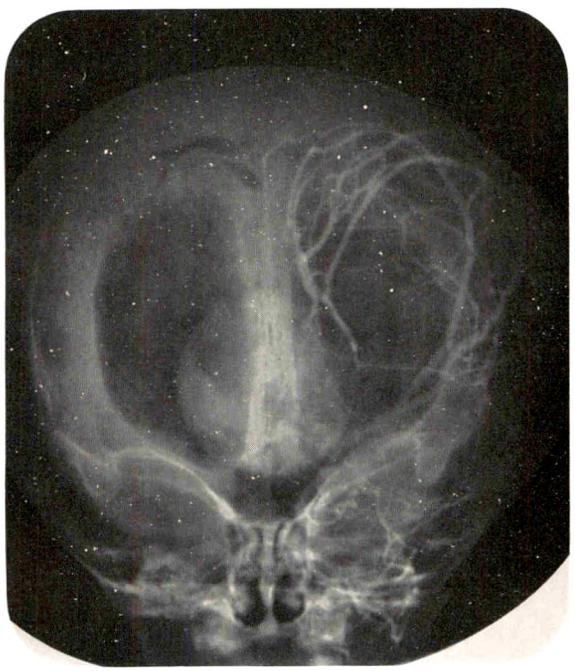
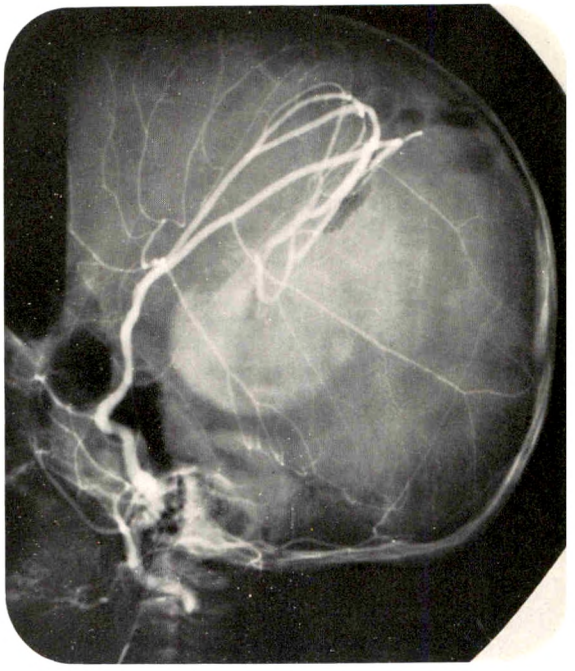


Figure 1. Enlarged head with dilated scalp veins.





Figures 2 and 3. Preoperative anteroposterior and lateral combined arteriograms and pneumoencephalograms show, in an early arterial phase, large middle cerebral branches extending over left cerebral hemisphere, and opacification of a large aneurysm of the vein of Galen. (See Figure 9—next page. Note

ANEURYSM OF VEIN OF GALEN *(continued)*

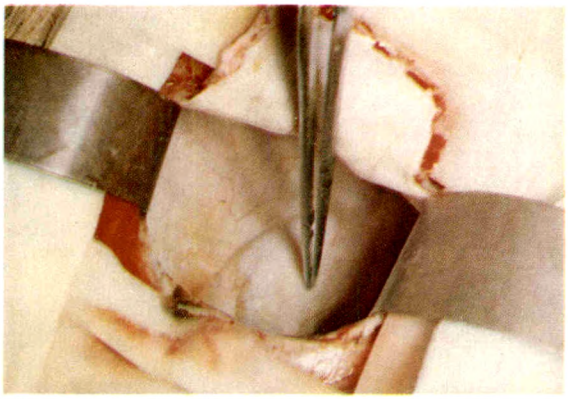


Figure 4. Surface of arteriovenous sac.

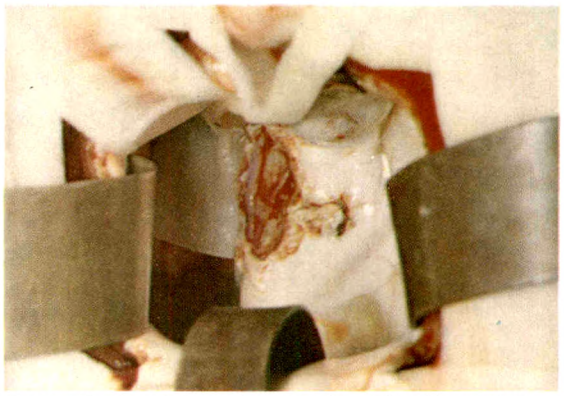


Figure 5. Arterial supply on surface of malformation.

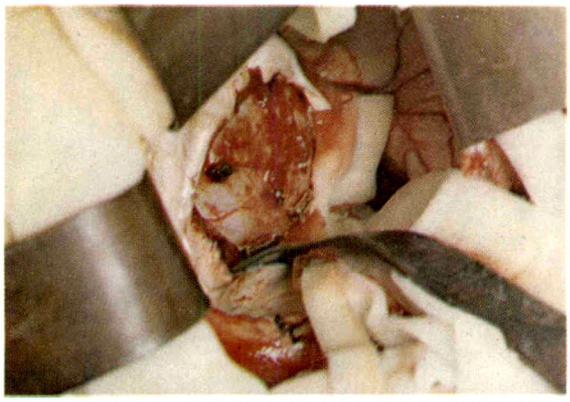


Figure 6. Arterial supply clipped on surface of malformation.

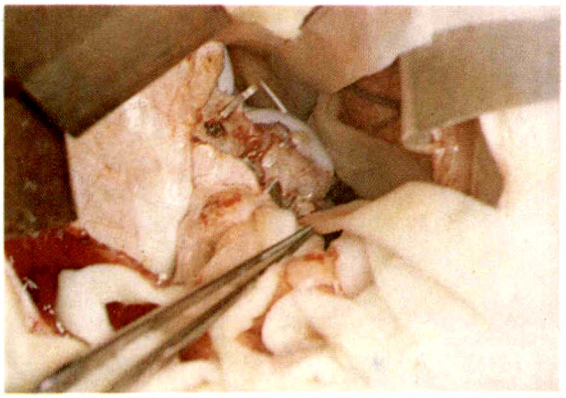


Figure 7. Venous sac collapsed after occlusion of supply.

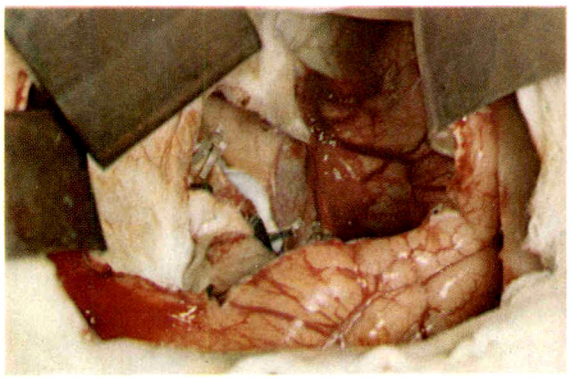


Figure 8. Ventricular obstruction now relieved.

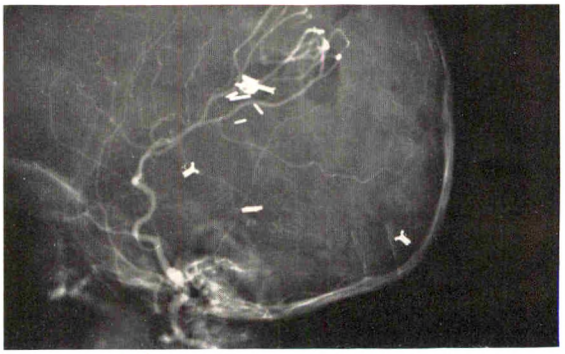
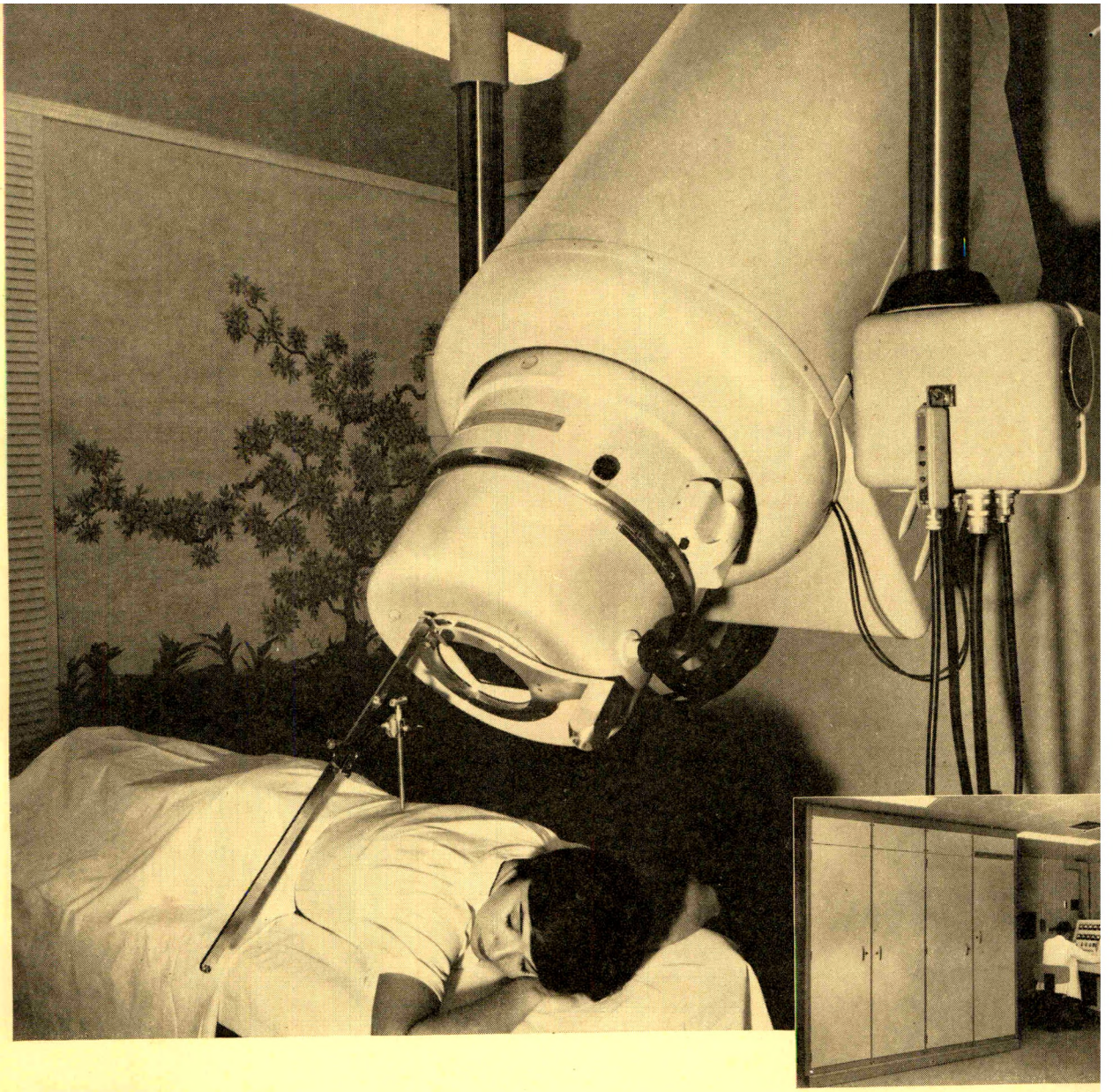


Figure 9. Postoperative left carotid arteriogram showing surgical clips used to occlude arterial supply as well as to plicate the aneurysm.

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